Drug eruptions; a clinical study on the irritant effects of drugs upon the skin / [Prince A. Morrow].

IODIDE OF POTASSIUM ERUPTION.

H. BENCKE, LI

DRUG ERUPTIONS

A CLINICAL STUDY

OF THE

IRRITANT EFFECTS OF DRUGS UPON THE SKIN

BY

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PREFACE.

THE general proposition that the physician should be familiar with the effects of every drug that he employs in the treatment of disease is axiomatic. He should not only be acquainted with the drug's normal, typical mode of action, but also with its abnormal or incidental effects, the more especially since, in the case of drugs as in the phenomena of every-day life, it is often the unexpected that happens.

The abnormal phases of drug action are comparatively an unexplored field. While it has long been known that eruptive disturbances of various kinds may result from the use of certain drugs, yet the number of drugs in common use capable of causing cutaneous disorders, the clinical appearances which they present, and the conditions which influence their development, are not sufficiently familiar to the profession.

The changes in the skin caused by drugs derive a special practical interest from the fact that they sometimes simulate very accurately the eruptive fevers and other idiopathic affections of the skin, and it is important that the physician should be able to differentiate the clinical

features, and correctly interpret the pathological significance of phenomena so widely different in their mode of origin.

It is only within the last few years that this subject has received much attention from the profession. When the enormously large number of cases of drug eruptions which have been recently reported is contrasted with the comparatively few formerly recorded, it is evident that a prolific cause of cutaneous disorders long escaped recognition.

No doubt the reason that drug eruptions have been signalized so much more frequently within the last few years is attributable to the more exact methods of modern observation, the greater care and precision with which etiological factors are traced, and the recognition of the influence of numerous pathogenetic agencies which formerly were not suspected to be the originators of morbid changes in the skin. A mine of etiological agencies in the production of cutaneous disorders has been discovered, not only in the case of drugs, but also in the vaccine virus, mental emotions, traumatism, menstruation, septicæmia, pyæmia, glycosuria, etc.

It is not proposed in this work to study the cutaneous action of all drugs which have been accredited with the property of producing eruptive disturbances. The list is a long one, and embraces many agents which are not in common use, and a consideration of their dermatopathic effects would be lacking in practical value.

The relations which these cutaneous phenomena bear

to the drug's physiological action and to conditions of individual susceptibility have not been definitely determined. In the present state of our knowledge, a satisfactory solution of the problem is perhaps not possible. We know little definitely of the laws of drug action, and still less of the conditions which govern individual susceptibilities.

The author's object has been to collect from all available sources well authenticated observations relating to every form of cutaneous disorder thus far recorded from the action of drugs. To these have been added numerous personal observations, some of which have been already published, and others appear now for the first time.

It is hoped that these results will prove of value to the general practitioner, not only in directing his attention to the large number of drugs in general use capable of causing eruptive phenomena, but in familiarizing him with their clinical appearances, so that he may be enabled to recognize and refer them to their true cause when occurring in his own practice.

The author desires to acknowledge the invaluable assistance of his friend, Dr. Charles Rice, who has furnished a series of valuable tests for the detection of drugs in the urine. As most drugs are chiefly eliminated through the kidneys, a knowledge of the processes to be employed for their detection cannot fail to be of value from a diagnostic point of view.

The various sources from which the clinical facts embodied in this work have been gleaned are acknowledged

in the General Bibliography, and in the Special Bibliography of individual drugs, which will be found appended. The references are arranged in the order in which they are quoted.

66 West 40th St., January 1st, 1887.

DRUG ERUPTIONS.

HISTORY.

THE literature of drug eruptions is essentially a new literature. While a few individual observations respecting the irritant effects of drugs upon the skin are found scattered here and there in the older medical literature, it is only comparatively recently that drug eruptions have been recognized as a distinct and clinically important class of affections. Most writers on Materia Medica and Therapeutics have passed over in silence the cutaneous manifestations of drug action, or have treated of them superficially and as of no practical importance. They were for a long time practically ignored by dermatologists, and it is only in the most recent text-books that they have been assigned a distinct place in the category of the dermatoses.

Lorry was the first dermatologist who called attention to the production of eruptions from the use of drugs. In his treatise, entitled "Tractatus de morbis cutaneis" (1777), he says: "I have had many times occasion to observe in the course of my practice pruriginous, squamous, and miliary eruptions accidentally determined by the use of aromatic medicines, sudorifics, essential oils, etc."

Bell (1796) first described the irritant action of mercury

upon the skin in the production of *eczema mercuriale.* Alley (1804) gave a more detailed description of the cutaneous eruptions caused by this drug, the accuracy of which a more extended observation has amply confirmed without adding much to its completeness.

Montègre (1814) described an eruption of urticaria from the ingestion of copaiba. Since then, many other forms of eruptive disorder due to this drug have been noted.

Rayer (1835) recorded numerous observations relating more particularly to the eruptive disorders caused by external irritants, which were classed by him as "artificial eruptions."

Ricord (1842) described various forms of eruptive accidents produced by iodide of potassium, the list of which has been largely increased by subsequent observers.

Devergie (1857) called attention to the eruptive disturbances caused by arsenic. We are, however, chiefly indebted to the admirable thesis of Imbert-Gourbeyre for our knowledge of the irritant action of arsenic upon the skin.

Bazin (in his "Leçons Théor. et Clin. sur les Affections Cutanées Artificielles," 1862) made a systematic study of the cutaneous disorders provoked directly and indirectly by the action of drugs, and grouped them according to their elementary lesions.

Since then, numerous observers, more particularly Bérenguier and Deschamps in France, Lewin and Behrend in Germany, Farquharson and Hutchinson in England, Piffard, Van Harlingen, and others in this country, have made a study of drug eruptions, and have added materially to our knowledge of their clinical characteristics, course, and pathogenesis.

DEFINITION.

In examining the literature of "Drug Eruptions," there is found a difference in the signification of this term as employed by different writers. By many, changes in the skin caused by the external contact of drugs are excluded from this category, and the list embraces only those eruptive phenomena which follow the internal administration of medicines and are connected with their absorption and elimination. Obviously, however, there is no well-grounded distinction between pathological effects determined by the same cause of action. In the case of many drugs, identical changes in the skin follow indifferently their external or internal use, and these changes are not always limited to the portion of the integument with which the drug comes in immediate contact, but may be manifest on parts remote from the point of application. They are in many instances consecutive to the absorption of the drug, and are an expression of its constitutional action.

By others, the term has been limited in its application to the anomalous or incidental effects of drugs upon the cutaneous surface, in contra-distinction to changes in the skin which are a more or less constant expression of the drug's physiological action, and which may be provoked for therapeutical purposes; evidently, however, a distinction based upon *motive in prescribing* is as fanciful as it is unscientific. The acneiform eruption of bromide of potassium, for example, occurs in a large proportion of all cases in which the drug is used, and its appearance is regarded by many authorities as the necessary evidence that the full therapeutic efficacy of the drug has been obtained. Although *designedly* produced, it is none the less a drug eruption. Individual peculiarity plays so impor-

tant a rôle in modifying the action of drugs that it is impossible to closely differentiate normal and specific, from unexpected and anomalous effects.

In the proper signification of the term, Drug Eruptions *embrace all congestive and inflammatory changes in the skin caused by the external or internal use of drugs.* This definition includes all eruptive disorders caused by external contact, as in industrial pursuits, intentional application to secure revulsive action, or for purposes of simulation, as well as those resulting from the introduction of drugs into the system by absorption from the mucous membranes, the skin, or cellular tissue. The effect is the same, no matter through what channel of entrance the drug has gained access to the system.

CLASSIFICATION.

A classification based upon the anatomical form of the lesions produced by drugs is impracticable. The very multiformity of the lesions forbids such an attempt, for, while the irritant action of a particular drug may in one individual be manifested by a single elementary lesion, the same drug may produce in another individual eruptive elements of dissimilar forms.

Bazin, applying the natural classification of Lorry to drug eruptions, divided them into two classes: *affections provoquées directes*, caused by the direct application of drugs upon the integument; and *affections provoquées indirectes ou pathogénétiques*, including under this head every eruption produced by the introduction of a medicinal substance into the organism by way of absorption.

Under the title of "hematogenetic exanthemata," Behrend has classed drug eruptions as follows; 1st, eruptions occasioned by the specific action of drugs—acute in char-

acter; 2d, eruptions caused by the elimination through the skin of certain drugs—chronic in character; 3d, eruptions caused by the dynamic action of drugs, which are, like the first class, acute in their development and course, but appear to possess a certain period of incubation.

In this work, no classification will be attempted. The list of drugs will be taken up in alphabetical order, and the cutaneous phenomena exhibited by each will be examined in succession.

GENERAL CHARACTERISTICS.

The symptomatology of particular drug eruptions will be considered under the head of each individual drug. Certain characteristics common to them as a class may be referred to in this connection.

While it is not possible to formulate with absolute precision the distinctive characters of drug eruptions, or indicate definite features by which they may in every instance be recognized, and at once differentiated from the idiopathic affections of the skin, yet they possess certain special attributes which stamp them as a separate clinical class.

The polymorphism of drug eruptions constitutes a distinctive feature. Every possible lesion of the skin—macules, papules, wheals, tubercles, vesicles, bullæ, pustules, furuncles, ulcerations, gangrene, etc.—have been observed as the direct result of the use of drugs.

The Rapidity with which the Eruption Develops.—Eruptions provoked by external irritants usually make their appearance within a few hours after the application of the exciting cause. The intensity of the resulting dermatitis depends upon the nature and strength of the irritant, the duration of its contact, and the sensitiveness of the skin.

The difference in the susceptibility of the skin of different individuals to external irritants is markedly shown in relation to arnica, poison ivy, etc.

The length of time which intervenes between the ingestion of drugs and the first appearance of the eruption also varies according to the nature of the drug, the quantity administered, and the predisposition of the individual.

In general it may be said that certain forms, especially the erythematous and exudative, come out rapidly, from a few minutes to several hours after the ingestion of the drug, and vanish with the same celerity with which they appeared, if the offending agent be withdrawn. In other cases, it may require repeated and long-continued use to develop the irritating effect upon the skin. In still another class of cases, small doses—smaller, indeed, than are required to produce the ordinary physiological effect of the drug—promptly determine violent tegumentary disturbance. It is noteworthy that, in exceptional cases, large doses of the same drug in the same individual may occasion no such effect. In these cases, there would seem to be a reversal of the material law that increase of quantity carries with it multiplication of power. In the case of eruptions which are common and typical, so to speak, which occur in a large proportion of all cases in which the drug is administered, as iodic or bromic acne, there is a measurable relation between the quantity of the drug ingested and the extent and severity of the lesions. In a majority of cases, however, the quantity of the drug ingested is immaterial, its irritative effects upon the skin being determined rather by the idiosyncrasy or susceptibility of the individual.

Form.—Drug eruptions differ in form and degree of severity from the simple fugitive hyperæmia which rapidly fades, seeming to impress the skin so lightly that it leaves

no trace, to the most violent inflammation, terminating in desquamation, sometimes exfoliation of the epidermis in large lamellæ or flakes.

The eruption caused by many drugs has a special form, not absolute and unvarying, but sufficiently so to be regarded as typical. This is especially the case as regards the irritant effects caused by the external application of drugs. The lesions caused by chrysophanic acid, tar, croton oil, tartar emetic, for example, are pathognomonic, so to speak. We recognize the character of the agent by its peculiar local action upon the tissues.

The eruptions determined by the internal use of many drugs is also characteristic; thus the eruption of belladonna is scarlatinoid; that of antipyrine, measly; that of the bromides, papulo-pustular. But it is well to remember that, coincident with this more common and characteristic form, there may be an accessory group of quite different eruptive elements which may indeed substitute or take the place of the former. The multiplicity and variety of forms caused by the same drug depend, not so much upon the quality of the generative agent, as upon the mode of reaction of the individual, and upon other conditions imperfectly understood.

Locality.—The effect of irritants externally applied is usually limited to the parts exposed to direct contact, as the face, hands, and forearms, or to the vascular areas supplied by the affected nerves. Sometimes, however, the eruption overleaps these limits and is manifested on parts distant from the original focus of irritation. Certain regions are more susceptible than others to irritant influence, such as the face and genitals, and, indeed, wherever the skin is thin and delicate and rich in its nervous and vascular supply.

The eruptions caused by the internal use of drugs may

be localized or generalized over the entire surface. There are certain regions affected from preference by individual drugs, upon which the eruption first appears, and from which it last recedes. The eruption is by no means limited to these predilected regions, they simply constitute points of departure from which the eruption becomes generalized if the use of the drug be persisted in. These peculiarities of localization will be noticed when considering the action of individual drugs.

The course of the eruption varies: sometimes after attaining a certain development it persists in this form, and the indefinitely prolonged use of the drug provokes no additional phenomena. This is especially true of the acneiform eruption from bromide of potassium, which may remain, practically unchanged, for weeks or months. In the majority of cases, however, the eruption becomes, under the continued use of the drug, intensified in extent and severity, and new eruptive features may be added.

It is a noteworthy fact that the principle of *accoutumance*, by virtue of which the tissues become, from frequent exposure to any irritation, insensible to its action, does not come into play here. The textural predisposition of the skin to irritant action is not exhausted by habituation; on the contrary, it seems more quick to take offence at each new exhibition of the drug.

It has been observed that one attack of a drug eruption seems to confirm and intensify the susceptibility to subsequent attacks. While it may have required long and continued doses to determine the eruption in the first place, much smaller doses suffice to promptly redevelop a succeeding outbreak. There are rare cases on record in which this susceptibility has been overcome, or temporarily extinguished, by large and massive doses.

In the case of persons who are exposed to external irri-

tants, such as workers in quinine manufactories, in industrial occupations where arsenic and other poisonous dyes are used, it has been observed that the skin, though remonstrating by signs of irritation at first, acquires a certain immunity by habituation, so that the avocation can be pursued without serious inconvenience. It is to be noted, however, that this acquired immunity is readily lost if the person should cease his occupation for some time; upon resuming it, the skin again protests, and immunity must be repurchased at the expense of more or less irritation for a variable time.

The duration of the eruption is usually sharply proportionate to the continuance of the exciting cause. While in some cases it may come out for some time after the use of the drug has been suspended, yet, ordinarily, improvement begins immediately upon the withdrawal of the offending cause. Its more or less rapid involution depends, of course, upon the character of the lesions and the recuperative powers of the individual. In certain diathetic conditions, when a latent predisposition to cutaneous disturbance has been awakened into activity by the drug, the eruption may persist indefinitely.

The subjective sensations which usually attend drug eruptions vary in intensity according to the nature of the inflammatory element. Sensations of burning, tingling, and the most intolerable itching are generally present, especially preceding the outbreak of the eruption and during its acute stage; in rare cases, the eruption is completely indolent, and determines scarcely any subjective disturbance—the totality of the symptoms being expressed in the objective phenomena.

Drug eruptions are often accompanied by what are recognized as the ordinary physiological effects of the drug. Sometimes, however, the changes in the skin are

attended with a set of additional symptoms which have nothing to do with the drug's normal action, such as fever and constitutional disturbance, more or less severe headache, and a general feeling of malaise.

If the use of the drug be persisted in after indications of intolerance have declared themselves, both the subjective and objective symptoms become intensified, the whole system may sympathize, and a high grade of constitutional reaction be manifested. In some extreme cases, in which there is necrosis of the tissues and more or less profound ulceration, death may result from exhaustion.

ETIOLOGY.

Etiology is commonly considered the weakest, as well as the most difficult chapter of pathology. In the study of the causation of drug eruptions, we have not to deal with mysterious agencies too subtle to be seen or demonstrated, and the nature of which can only be judged by their effects; the exciting cause of drug eruptions is material and tangible, and in the majority of cases this important element may be eliminated from the list of unknown quantities.

The nature of the exciting cause is ordinarily readily apprehended by the physician, or, in some cases, suggested by the patient, whose perceptions may have been enlightened by a previous similar experience, or who may be quick to grasp the relation of cause and effect between the ingestion of a drug and the disturbance which oftentimes swiftly follows. In most cases, if there be any doubt as to the causal connection between the drug and the eruption, it is resolved by a comparatively brief expectancy, for, as Bazin has remarked, in no other class of affections is the application of the old adage, *sublata causa, tollitur effectus,*

so signally appropriate as here. Not only may the *quality* of the exciting cause be appreciated, but, unlike other causes of disease, its exact *quantity* may be definitely determined. It must be admitted, however, that in many drug eruptions the result is entirely independent of conditions of quantity, as it follows indifferently large or small doses.

If the efficient cause of drug eruptions be easily apprehended, the remote or predisposing causes still remain to perplex and baffle the physician; especially is the problem complicated by the existence of that etiological unknown—idiosyncrasy. Precisely as in the operation of other causes of disease, we find that susceptibility to the irritant action of drugs varies in different individuals and under different conditions. The predisposing causes, such as climatic conditions, age, sex, heredity, etc., which exert such a modifying and controlling influence over the production of skin affections in general, play a rôle of minor importance here.

As regards the influence of climatic conditions, it has been observed that drug eruptions are more common in the summer season when the cutaneous functions are in the highest state of activity, and we may assume that all conditions which favor a fluxion to the surface predispose to the production of certain forms of drug eruptions.

The use of alcohol, teas, hot drinks, etc., which stimulate the cutaneous vascular system, are found to exert a marked influence in the production of the chloral rash, for example.

Age and sex seem in no way to dispose the skin to the irritant action of drugs, except from the accident of peculiarities of anatomical structure. As is well known, the texture of the skin of women and children is much less dense and tough than the same organ in man. This

greater relative fineness and sensitiveness of the skin renders it more susceptible to take on morbid action, and thus more liable to eruptive disorders from any cause of irritatation. It must be admitted, however, that the often-observed relation between a fine organization of the skin and its susceptibility to irritant influences is by no means constant. We sometimes find that persons with thick and opaque skins manifest a peculiar aptitude to eruptive disorder, while persons with thin, transparent skins are not at all liable to such disturbance.

Blond children with fine, delicate, succulent skins are especially liable to eruptive disturbances from the use of drugs, and, besides, the skin of all children is more irritable and prone to disorders of circulation from reflex disturbances.

Nervous irritability, hysteria, spinal irritation, and other neuroses which, from some unknown peculiarity of organization, are much more common in women than in men, constitute what may be termed a neuropathic predisposition, which markedly modifies the action of drugs.

The comparative influence of heredity as a predisposing cause to drug eruptions is probable from the fact that idiosyncratic intolerance of drugs is rarely an acquired peculiarity. Observations bearing upon this point have not been collected in sufficient number to warrant deductions of a positive character.

Diathetic predispositions exert a marked influence in determining drug eruptions. This has been especially observed in the case of local irritants, the eruption becoming generalized and persisting long after the exciting cause has ceased to act. In these cases, it is probable that the drug would be without pathogenetic influence, were it not for the predisposition to eruptive disorder constituted by the peculiar diathesis, the existence of which is a necessary

condition of its operation. Eczematous subjects are particularly prone to drug eruptions. Numerous cases are recorded in which the slightest exposure to external irritants, such as arnica, carbolic acid, etc., has provoked into activity a latent eczema.

Scrofulous and lymphatic subjects are peculiarly prone to eruptions from the ingestion of drugs, which, it has been observed, are apt to be of a pustular character.

The most powerful predisposing cause of the determination of the irritant effects of drugs towards the cutaneous surface is the physiological predisposition known as *idiosyncrasy*. While the term is intrinsically meaningless, yet it is convenient to express that abnormal susceptibility to external impressions which is manifest in certain individuals—a condition which has been regarded as inexplicable as it is mysterious. The existence of idiosyncrasy as an etiological factor has been accepted as an ultimate fact, unknown and unknowable.

While we may not be able to draw aside the veil which shrouds this "mystery of individuality," yet it should not be allowed to obstruct what light may be thrown upon the explanation of its phenomena from our knowledge of the physiological properties of the tissues and their mode of reaction to external impressions.

Idiosyncrasy has been termed the bugbear of therapeutics; but this factor, as influencing the action of drugs, is no more mysterious than the predisposition which is manifest in relation to the action of other exciting causes of disease, and which determines the morbid effect to this or that particular organ. To take a familiar example: of a certain number of individuals exposed to the action of cold, as in wetting the feet, the morbid impression may be reflected upon the respiratory mucous membrane, producing in one case sore throat; in another, bronchitis; in an-

other, pneumonia or an attack of asthma; or it may be reflected upon different tissues altogether, producing in one case neuralgia; in another, rheumatism; in another, congestion of the kidneys, etc.; the same morbid influence determining disease of a particular organ, varied in form and intensity, or even different diseases. In the explanation of the mode of production of these phenomena, we assume the existence of a textural predisposition in the affected tissues, constituted, it may be, by inherent weakness or antecedent disorder, which renders them *partes minoris resistentiæ.*

So, also, the determination of the irritant action of a drug towards the cutaneous tissue implies either the existence of structural peculiarities of the skin, enfeebling its capacity of resistance, or a heightened susceptibility of the nerves which regulate the circulatory and nutritive processes of this organ. It is by no means clear whether this morbid aptitude of the skin to irritant action is due to anatomical or histological alterations in the cutaneous tissues, too subtle to be seen or demonstrated, or to an abnormality of the nerve element, which may be expressed as "erethism" or "irritability."

Begin defines idiosyncrasy as "the predominance of an organ, a viscus, or a system of organs." Experimental investigation has demonstrated that "the law which governs the susceptibility to the action of drugs is, that, the more highly specialized any system is, the more readily it is affected by a medicinal agent." We find in persons most susceptible to anomalous eruptions that the nervous element or temperament predominates. Neuropathic, hysterical individuals, those who suffer from any of the protean forms of neurasthenia, are precisely the persons most liable to manifest idiosyncratic intolerance of drugs.

Conjoined with this highly-wrought nervous organiza-

tion, the skin itself may be more highly differentiated by fineness and delicacy of structure, and endowed with a more exquisite sensibility.

We may conclude then that a predisposition to drug eruptions may inhere in the skin from some congenital structural peculiarity constituting a "native debility" of this organ, or it may reside in a peculiarity of the nervous organization, characterized by an abnormal sensitiveness of the vaso-motor system to irritant influences.

PATHOGENESIS.

There is a difference of opinion among writers as to whether these eruptions should be classed among the physiological or toxicological effects of the drugs producing them. The term pathogenesis, implying a pathological process, is employed with a clear recognition of the close lines which unite the physiological and the pathological. As pathological states are but modifications of the healthy state, so the toxic effects of a drug differ in degree, but not in essential nature from its physiological effects: there is no definite limit where the one ends and where the other begins. A certain proportion of drug eruptions are an expression of the drug's physiological action, while others are altogether incidental, depending upon conditions of the organism, which in the present condition of our knowledge are obscure and imperfectly understood.

Eruptions from the External Use of Drugs.

Excluding from consideration the class of agents known as escharotics, we will first briefly refer to the changes in the skin caused by the external application of certain drugs. The links in the relation between cause and effect are here distinctly traceable, and the mechanism of their

action is explicable on purely physical and chemical grounds. The intensity and severity of the congestive and inflammatory disturbance produced depend upon the nature of the agent employed, the duration of its contact, and other circumstances, such as the sensibility of the skin and the mode of reaction of the individual. Certain effects, to be considered later, are the result of the absorption of the drug through the skin, and analogous to those which follow its internal administration.

A clinical distinction may be made between effects which *invariably* follow contact with certain drugs and those which are *occasional and irregular* in their manifestation.

The *first class* of effects is determined rather by the nature of the drug than by any peculiarity of organization or mode of reaction of the skin. They are so constant and characteristic that we may recognize the nature of the agent employed by the form of its lesion. The blebs of cantharides, the pustules of antimony and croton oil are characterized each by a special evolution, and are as typical in their forms as are the pustules of variola. We cannot explain why the irritating influence of different drugs are exerted upon different constitutent elements of the skin, any more than we can explain why the pathological changes met with in measles should be grouped around the blood-vessels and glands, while in scarlatina the pathological process affects the tissues proper of the derma, as well as the cells of the epidermis.

In general, it may be said that the effect of a cutaneous irritant is limited to the vascular area supplied by the affected nerves. The irritating effect may sometimes pass beyond this limit and invade adjacent portions of the skin, or it may be diffused over the entire surface. This may be explained by what has been termed the "contagion of

continuity," or upon the assumption that it is due to the absorption of the drug and is an expression of its constitutional action.

The *second class* of effects is far from being constant. Their production seems to depend less upon the intimate nature of the exciting cause than upon a specific predisposition of the cutaneous tissues to disordered action, which may be expressed by the term *morbid aptitude*.

As in the case of anomalous eruptions from the internal use of medicines, the eruptive form is determined rather by the individual than by the drug. Thus we recognize in "tar acne" the specific irritating effect of tar upon the cutaneous tissue; but in one individual the use of tar may produce a simple dermatitis; in another, erysipelas; in another, a pustular or a furuncular inflammation; while in the large majority of individuals it will cause no eruptive disturbance whatever, the difference of the effect depending upon the reaction of the skin in the different individuals.

This variation in susceptibility to irritant influences of the skin of different persons may depend upon physiological conditions, such as a greater fineness or delicacy of texture, or upon a peculiar excitability or irritability of the sensory nerves, which disposes them to take offence at the slightest provocation. We find that this vulnerability of the skin which renders it abnormally incapable of resisting disturbing influences is manifest in relation to poison ivy, vegetable parasites, the exciting causes of eczema, and, in fact, all external irritants.

The cutaneous changes caused by the external application of drugs admit of a simple explanation. The drug acts, just as caloric or mechanical irritants do, upon the nerve element alone, the resulting changes being phenomena of irritation. The irritation of the peripheral ex-

tremities of the sensory nerves causes a paralysis of the vaso-motors of the vascular area affected, which results in dilatation of the blood-vessels, and which may go on to typical inflammation of the skin with exudation.

In the first class of cases, the specific character of the irritant determines the eruptive form ; in the second class, the response to the stimulus is materially modified by the physiological properties of the tissues affected.

Eruptions from the Internal Use of Drugs.

We come now to a consideration of the cutaneous disorders which result from the introduction of drugs into the system by way of absorption. Instead of a direct irritant influence upon the skin, the drug stimulates all the blood-containing organs with which it comes in contact. It affects the centres of sensibility as well as the peripheral nerves, and the pathogenetic mode is much more mysterious and difficult of comprehension.

The eruptive disturbances which follow the internal use of drugs may be divided into two classes :

1st. *Common, specific eruptions* which are more or less characteristic in their anatomical form, mode of development, and locality affected, and which are associated with the other physiological effects of the drug.

2d. *Incidental, anomalous eruptions* without distinctive form or character, which manifest dissimilar eruptive elements, and which may be associated with the physiological effects of the drug, or merely incidental thereto.

Eruptions of the first class, of which "bromic acne" may be taken as the type, must be regarded as an expression of the specific action of the drug upon the cutaneous tissues, as much so as its other physiological effects upon the general system. They occur in a large proportion of all

cases in which the drug is administered, and they are evidently determined by the inherent properties of the drug.

Eruptions of the second class must be considered as an aberration of the drug's normal action, the deviation from the typical mode of action being determined by the forces of the organism through which it operates. They may be caused by drugs which neither commonly nor specifically act upon the skin, the necessary condition of their development being a predisposition or aptitude inherent in the individual.

In this connection, it may be well to recall some of the more characteristic features of drug eruptions. In the first place, it must be borne in mind that the same eruptive form may be produced by different drugs, and that the same drug may produce a variety of eruptive forms. It is not possible, therefore, to establish a distinction between these classes based exclusively upon the anatomical form of the lesions, since one drug may exhibit characteristics of both classes. Thus the type of the quinine exanthem is erythematous, but exceptionally it may be eczematous or purpuric. Iodide of potassium ordinarily produces a papular or pustular eruption, but instead, or indeed coincident with this specific form, there may be an anomalous eruption of dissimilar forms. In cases reported by Pellizari and myself, for example, side by side with the common acneiform eruption there were bullæ, tubercles, ecthymatous pustules, and large subcutaneous nodules, which evidently must be classed among the rarer incidental effects of the drug.

Again a drug eruption, the type of which is erythematous, may, under special conditions, such as the prolonged continuance of the exciting cause, be developed into a papular, vesicular, or pustular eruption.

In other cases, there is no mutation of forms, the indefinitely prolonged use of the drug will be unattended with any essential change in the character of the eruptive element. If it commence as a papular or a pustular eruption, it will continue as such, independent of the dose or duration of the drug. It is to be noted, however, that when the lesions are in process of involution, if the drug be renewed, it will cause a *poussée subintrante*, and we may have different forms side by side, some in active evolution, others representing the acme or completion of the morbid process, while others are on the point of disappearance.

We perceive, then, that in endeavoring to appreciate the mode of production of these eruptions, it is impossible to adhere closely to the distinction between specific and anomalous eruptions, since there is nothing absolutely constant or characteristic in their respective forms; they are as varied in their manifestations as are the physiological peculiarities of the individuals producing them. It is to be observed, however, that difference in effect does not necessarily imply difference of mode of impression. We think that most writers err in attempting to differentiate pathogenetic modes upon the basis of difference in anatomical form of the lesions. Anatomical form is as misleading in pathogeny as it has proven defective as a basis of classification.

Notwithstanding the diverse character of drug eruptions as indicated above, we have seen that they all possess one distinctive generic feature, which stamps them with the seal of a common causality of origin—they always promptly disappear on the withdrawal of the exciting cause. The more or less rapid removal of the cause is of course subordinate to conditions of elimination; the celerity of this process varying in the case of different drugs. The rapidity of the disappearance will also vary

according to the nature of the lesions; obviously the slight cutaneous disturbance expressed by a simple erythema would not require the same time for its involution as the more profound tissue changes represented by an inflammatory nodule or an ecthymatous ulcer. Again, it is to be borne in mind that diathetic predispositions awakened into activity by an irritant drug may impress the character of chronicity upon the resulting skin lesions—the inflammatory fluxion to the surface persisting long after the cause which determined it has ceased to act.

Leaving out of consideration for the present that mysterious factor expressed by the term idiosyncrasy, let us examine the various theories which have been put forward as to the mechanism of the production of these eruptions.

In the first place, it may be said that an explanation of these incidental cutaneous phenomena has been sought for in the *quality of the drug*. It was naturally inferred that the production of unusual drug effects must be caused by an impurity of the agent used, due to its faulty mode of preparation or its accidental admixture with toxic principles, etc. With this view, other preparations of the same drug have been substituted, the alkaloid for the crude drug, and *vice versa*, with the result of the production of identical irritant effects upon the skin. So that the assumption of a possible impurity of the drug as the efficient cause of these irritant effects upon the skin must be dismissed as groundless and disproved by careful experimentation.

The theory which has been adopted by most writers on this subject is, that a large proportion of these eruptions are caused by the elimination of the drug through the skin.

The theory of the elimination of drugs through the cutaneous glands is based upon the assumption of the ex-

istence of one of two conditions as determining causes: 1. *Impairment of the integrity of the eliminating organs.* 2. *Elective affinity of the drug for the constituent elements of the glands.*

The hypothesis of the impairment of the integrity of the eliminating organs as a determining cause, is based upon the view that since almost all drugs introduced into the system are normally eliminated by the kidneys, when from any cause this channel of egress is blocked up, the skin by virtue of its vicarious functions attempts to perform the work of the kidneys, and the drug in its passage through the cutaneous glands causes irritation, which is manifested by various lesions. This theory, which has been urged with some plausibility by Farquharson, seemed to gain support from clinical facts. Several cases were cited in which the use of the bromides and iodides caused severe cutaneous disturbance, and the patients were found suffering from renal inadequacy and cardiac lesions. But further clinical inquiry has not demonstrated anything like a constant relation of cause and effect between severe renal disease and a special liability to a determination of drug action towards the cutaneous surface, even where the pathological alterations were of such a nature as to incapacitate these organs for the proper performance of their functions.

This theory pushed to its legitimate conclusion would attribute all drug eruptions to cumulative action, on the principle that introduction should in all cases be compensated for by elimination—the maintenance of this equilibrium being the condition of normal drug action. In other words, that "saturation of the system" with a drug must occur as a preliminary or necessary condition of the production of its incidental effects.

This assumption is, however, abundantly disproved by

clinical facts. We find that the smallest dose of a drug will, in many individuals, promptly produce the most violent tegumentary disturbance, while in others, massive doses of the same drug may be continued during long periods with absolutely no effect upon the cutaneous surface, the result being entirely independent of the *quantity* of the foreign element circulating in the blood. In the analogous cases of eruptive disturbance *ab ingestis* we recognize that it is the *quality*, not the *quantity*, of the irritant that offends.

Another phase of the "saturation of the system" theory is that the foreign material accumulates until nature, unable longer to tolerate its presence, concentrates her forces and makes a grand parturient effort to expel the offending material through the cutaneous pores, and in this process the skin suffers various lesions of continuity. This theory is akin to the now obsolete one which recognized in the roseola of syphilis, and the exanthem of the specific fevers, an evidence that the poison had been driven to the surface and was in process of expulsion.

The second hypothesis is that drugs have an affinity for special anatomical elements, and that, by virtue of this selective action, certain drugs are attracted towards the cutaneous glands. Physical and chemical evidence of this pathogenetic mode is furnished, it is claimed, in the anatomical seat of certain lesions, as the sebaceous glands in iodic and bromic acne, and in the demonstrated presence of the drug at fault in the lesions which it has caused. No absolute proof that either of these conditions is a constant occurrence has been adduced. While the follicular apparatus may be incidentally involved in any morbid process affecting the skin, there is no evidence that it is the exclusive seat of these lesions.

On the contrary, careful and minute investigations into

the anatomical seat of iodic and bromic lesions have shown conclusively that, in many cases at least, the sebaceous glands were unaffected. Drs. Thin and Duckworth concluded from their investigations of iodine lesions that they were not of the nature of acne; microscopical examinations showed no implication of the sebaceous glands and hair follicles. Negative evidence is also found in the fact that these lesions occur in cicatricial tissue, and in regions where sebaceous glands do not exist. Other observers have furnished positive proof that these lesions are of the nature of a localized dermatitis, in which the glandular structures may be healthy, or only incidentally involved.

Proof of the second proposition is also sought for in the fact that the drug has been found in the contents of certain lesions, detected in the act, so to speak. But absolute proof of the production of these lesions in this way cannot be adduced. So far from being a constant phenomenon, we are justified in regarding it as a mere accident or coincidence, since numerous observers have failed, even with the most carefully conducted tests, to detect the presence of the drug in the cutaneous lesions, while it was freely found in the urine. If the elimination of the drug through the glands be the cause of the disturbance, its presence should be a constant feature. Again, if the matter were reduced to a simple chemical combination between a certain drug and the glandular elements, then this action should take place every time and in every case where these two factors were brought into contact. On the contrary, instances are exceedingly rare in which such a reaction could by any possibility be alleged.

Trousseau sought to establish an identical pathogeny for sudoral and drug exanthemata, claiming that both were caused by a modification in the composition of the sweat,

which took on an irritant quality, and in its passage through the cutaneous emunctories, betrayed this irritation by a variety of pathological lesions. But proof that these lesions are not caused by an irritant and exaggerated sudoral secretion is found in the fact that two drugs, opium and belladonna, both produce a scarlatiniform eruption. The specific action of one is to stimulate the functional activity of the sweat glands, while that of the other is to diminish or suppress this function altogether. Further proof that eruptive disturbances are independent of the functional activity of these glands is furnished by the fact, that the existence of the condition known as unilateral sweating does not modify the symmetrical development of a drug exanthem. In a number of such cases reported, there was no difference in the rash on both sides.

Admitting that the eruptive disturbances which follow the ingestion of certain drugs are the result of modifications in the glandular tissues, associated with increased functional activity, we see in this only an evidence of the direct influence of the drug upon the special nerves which regulate the secretory functions of these glands. Recent physiological research has demonstrated the existence of special secretory fibres, which are distributed to the salivary and sweat glands, and which regulate their functional activity independent of conditions of hyperæmia. It has been conclusively shown by Sartisson that the absorption and elimination of iodine by the salivary glands, for example, is due, "not to chemical affinity of the drug for the substances of which the gland is composed, but to nerve influence alone," so that either functional or structural changes in the sweat glands point to a disordered innervation, the determining cause of which must be sought for in the action of the drug upon the special nerves which supply these glands.

The "elective affinity theory" must therefore be dismissed as improbable. There is no evidence that the cutaneous glands or other tissues of the body exert any influence upon drugs which is at all of the nature of attraction.

Behrend classes drug eruptions under the title of "Hematogenetic Exanthemata," on the theory that they are for the most part due to changes in the blood susceptible of clinical demonstration. He assigns special prominence to what may be termed the dynamic theory He asserts that all drug eruptions, with the exception of the erythemas caused by the specific action of belladonna, hyoscyamus, stramonium, and perhaps arsenic, and the acneiform and pustular eruptions commonly seen after the use of the bromides and iodides, more rarely after arsenic, are caused by the dynamic action of drugs. This effect, he claims, is entirely independent of the physiological and therapeutical action of the drug, but due to the agency of a foreign material, probably of chemical nature, generated in the blood by reason of the presence of the drug in the system.

Whether this foreign material is produced by catalytic action, or is the result of a direct combination of the drug with a hypothetical substance in the blood, is not specified. It is singular that this mysterious chemical compound should be so potent for mischief and yet so indefinite in substance that its detection transcends our powers of analysis. This hypothesis seems as fanciful as it is utterly untenable. It is merely a modification of the old humoralistic view which attributed all pathological alterations to a dyscrasic condition of the blood. Besides, this theory is irreconcilable with clinical facts. If the changes in the skin be caused by a changed blood mass, they should not

be confined to restricted localities, as is often the case, but should be manifest everywhere the blood circulates.

We come now to a consideration of the theory of the neurotic origin of drug eruptions—a theory which recognizes the intimate dependence of all cutaneous changes, whether slight and transient, or more profound and persistent, upon disorders of innervation.

While, at first glance, it may appear inconsistent to group together eruptions so multifarious in form and character, and attribute the same pathogenetic mode to drugs widely varying in their physiological action, yet there are many considerations which force us to the conviction that it is in the sphere of the nervous system that we must look for an explanation of these phenomena. In the light of our present knowledge respecting the primary action of most drugs upon the nervous system, such a pathogenesis of these eruptions is not only conceivable, but, reasoning from analogies with other cutaneous phenomena the neurotic origin of which has been demonstrated, it appears extremely probable.

The analogies existing between changes in the skin provoked by the direct contact of drugs and those resulting from their internal administration should not be ignored. Both classes of effects are due to the same cause of action; the inflammatory process is identical, and they exhibit the same eruptive elements. So far as the anatomical form of the lesions is concerned, there is no difficulty in attributing to them the same pathogenetic mode. We have seen that almost every possible lesion of the skin, erythema, papules, pustules, vesicles, bullæ, wheals, furuncles, gangrene, etc., may be determined by the application of external irritants. The mechanism of this production is simple and evident. There is no elimination of the drug through the cutaneous glands, no pos-

sibility of a changed blood mass, no generation of a "chemical compound" from the presence of the drug in the circulation.

The inflammatory changes in the skin are caused through the agency of the nerve elements alone. The irritant applied to the surface of the skin affects its sensory nerves, and the inflammatory phenomena appear in the vascular area which they control. Is it not fair to assume that precisely similar phenomena may result from a direct impression of an irritant agent circulating in the blood upon the vaso-motor centres or upon the peripheral distribution of these nerves?

In studying the symptomatology of drug eruptions, we find that a large proportion present the characters of simple cutaneous congestions, associated with sensory disturbances more or less severe. Usually the nervous symptoms precede the development of the exanthem.

These congestious appear suddenly, and may affect only certain cutaneous regions, or they may become generalized, according as the disordered innervation is limited to particular vascular areas or affects the entire cutaneous vascular system. The character of the changes impressed upon the skin will depend upon the blood-stasis, whether it be transient, or prolonged and intense.

In some cases, no doubt, these congestions are purely reflex phenomena, the point of departure of which is irritation of the sensory nerves of the gastro-intestinal mucous membrane. They are analogous to urticaria ab ingestis, and reflex changes in the skin from irritation of a peripheral nerve, as in traumatism. Besnier attaches considerable importance to this pathogenetic mode, and proposes to circumvent it by introducing the drug hypodermically. Unfortunately for this theory, it has been proven that the dermatopathic effect is, in the case of

most drugs at least, entirely independent of the mode of their introduction into the economy. It is probable that irritation of the terminal filaments of the pneumogastric accounts for but a small proportion of these cutaneous disturbances.

The large majority are consecutive to absorption of the drug, and due to its specific action upon the peripheral nerves or nerve centres. Whether this influence be exerted primarily upon the vaso-dilator or the vaso-constrictor nerves, the ultimate effect is vascular dilatation, and if the congestion be sufficiently intense, exudation. We recognize the erythematous and urticarial eruptions of antipyrine, arsenic, belladonna, bromide of potassium, chioral, copaiba, digitalis, hyoscyamus, opium, morphia, quinine, stramonium, salicylic acid, etc., as angio-neurotic phenomena, caused by the specific action of the drugs in question upon the vaso-motor system.

The similarity in these eruptions to other cutaneous phenomenon, the nervous origin of which is recognized, would argue similarity of pathogenetic mode. It is now accepted that the roseola of syphilis, the prodromal rash of variola, the exanthem of measles, scarlatina, typhoid fever, etc., are due to the direct action of an irritant, the specific virus of the particular disease, upon the centres which preside over vaso-motor innervation. We may reasonably infer a like nerve influence in the production of erythemas from drug action. The assertion made many years ago by Wilson that "the influence of the vaso-motors is involved in the production of roseolas," may be extended to embrace all cutaneous phenomena of a simple congestive character.

The more fugitive forms of drug hyperæmias present many striking analogies both in form and localization with that large class of eruptions known as mental or

emotional congestions, doctor's rash, which is so constant a phenomenon in the examination of nervous females, *erythema pudoris*, etc. These are pure angio-neuroses dependent upon an impression emanating from the emotive centres.

Clinical analogies with drug eruptions may also be found in traumatic, septicæmic, diabetic, and menstrual eruptions, the *taches cérébrales*, tabetic ecchymoses, etc., occurring in cerebral and spinal diseases, and which are absolutely inexplicable except on the theory of their neurotic origin.

We have seen that in many cases the severer forms of eruptive disturbance are the outgrowth of the simpler, the grade of the eruptive element depending upon the continuance of the morbid stimulus. There are certain other cases, however, in which the eruption is only developed after the more or less prolonged use of the drug, the structural changes having a definite relation to the size and continuance of the dose, such as the severer forms of the bromide and iodide eruptions, for example. The changes in the skin are often associated with the toxic systemic effects of the drug, known as "Iodism," "Bromism." In these cases, not only is there a change in the form of the inflammatory process in the skin, but in addition to the vascular pathological phenomena, there are nutritive or trophic modifications depending upon a profound constitutional disturbance.

While there is no doubt that the vaso-motor nerves modify to some extent the nutrition of the tissues to which they are distributed, yet in these severe forms, characterized by a disturbance of local nutrition more or less profound, another agency than vaso-motor innervation is apparently involved—they are probably due to an impression of the drug upon the trophic centres, which regulate nutrition.

Physiological research, as well as pathological facts, have demonstrated that the nervous system exercises a constant and controlling influence upon the nutrition of the tissues. Whether this influence is exerted through the nerves which regulate vascular supply, or whether there exist certain nerves with specialized functions which have been denominated trophic nerves, is immaterial to our present inquiry. The fact remains that a trophic influence is exerted upon the cutaneous tissue by the nerve centres, and that when any impression disturbs this regulating power, perversions of nutrition result. This disturbing impression may be made upon the nerve centres or upon the peripheral nerves. Peripheral irritations will cause reflex alterations of nutrition precisely as they cause reflex disturbances of motor functions.

The direct dependence of cutaneous lesions, varying in character and intensity from simple dermatitis to the profoundest changes in the skin and cellular tissue, upon alterations in the peripheral and central nerves, has been demonstrated by numerous anatomico-pathological investigations. The neuropathic origin of pemphigus, zoster, leprosy, symmetrical gangrene, decubitus acutus, mal perforans, ulcers of the leg, exfoliative dermatitis, and certain forms of eczema has been thus demonstrated. May we not reasonably infer a like pathogenesis in the case of drugs which are capable of exercising such a profound influence upon the nervous system?

The fact that structural alterations of the nerves, leading in many cases to abolition of their functions, have been found in the diseases just referred to, does not militate against this view. Physiological experiments have proven that molecular changes in the nerves, from excitations of transient influence, electricity for example, affect the nerve

functions precisely as do gross pathological changes of structure, or even section of the nerve.

While there is no positive evidence that drugs produce modifications of molecular arrangement, however minute, in the nerve tissues, yet it is a noteworthy fact that a large proportion of the medicinal agents which determine eruptive disturbances, act specifically upon the nervous system. Many drugs not credited with this physiological action undoubtedly exercise it. Proof of this proposition is found in the neuropathic character of the several groups of symptoms comprehended under the general terms, "iodism," "bromism," "cinchonism," "hydrargyrism," etc., with which the irritant action of the drugs upon the cutaneous surface is so often associated. All authorities recognize these manifestations as due to a disorder of the central nervous system, caused by the depressant action of the drug upon the brain and spinal cord. If the impairment of sensation of mucous membranes, formications, muscular tremors, troubles of intelligence, paretic phenomena, and other grave symptoms of "bromism" be manifestations of the effects of the drug upon the nerve centres, why is not the concomitant "bromic acne," with which these symptoms stand in intimate connection, likewise a neurotic phenomenon? It is irrational to separate the skin affection from the group of other symptoms which make up this clinical picture, and assign to it an entirely different pathogenesis.

The only correct interpretation of the physiological predisposition, known as idiosyncrasy, as a determining cause of drug eruptions is based upon a recognition of their neurotic character.

We may safely assert that so far as we can apprehend the nature of idiosyncrasy, as affecting the cutaneous action of certain drugs, it seems to depend upon a height-

ened susceptibility of the nervous system, associated or not with a specific predisposition of the cutaneous tissues to irritant impressions. In persons who manifest this idiosyncratic intolerance, the equilibrium existing between the skin and the nervous system in their vascular and nutritive relations is easily disturbed, the form and intensity of the resulting reaction being largely determined by the physiological properties of the tissues affected.

As is well known, the incidental effects of drugs may be manifest in other organs. The explanation of their more frequent determination toward the skin must be sought for in the sympathetic lines which unite the nervous and cutaneous systems. The skin is not only the receptive surface of all sensory modifications from the external world, but it is the principal medium through which the nervous system manifests its emotional and other disturbances.

Proof of the neurotic character of drug eruptions may also be drawn from the alterations of sensibility, with which they are associated; their symmetry; their generalization or their restriction to certain regions, according as the drug affects the general nervous system, or the special nerve centres which preside over particular cutaneous departments. Indeed, their very caprices and contradictions constitute a strong proof of their neurotic origin, suggesting a modification of the controlling, regulating influence exercised by the nerves upon circulation and nutrition.

DIAGNOSIS.

The diagnosis of the eruptions caused by the *external* use of drugs, whether from accidental contact, or intentionally applied for therapeutic purposes, is generally easy. The limitation of the irritation to the parts exposed to direct contact, which is commonly the case, and a knowledge of the specific forms of skin irritation which certain drugs almost invariably produce, is sufficient for a diagnosis. The black comedo-like points which characterize tar acne, for example, are pathognomonic. The peculiar staining of the hair and nails caused by chrysophanic acid, would at once suggest the explanation of a coincident inflammation of the skin. The pustules produced by croton oil and tartarized antimony present certain characteristics by which they can be differentiated from each other, and from other pustular lesions which have a different mode of origin.

The eruptions caused by the *internal* use of certain drugs derive their chief clinical importance from their resemblance to the eruptive fevers and idiopathic affections of the skin. The exanthem of quinine and belladonna bears a close resemblance to the rash of scarlatina, and when it is accompanied with fever and elevated temperature, the simulation is so perfect as to deceive the most skilful and practised observer. The copaiba eruption may resemble that of measles; this similitude is heightened by the irritant effects of the drug upon the mucous surfaces, causing redness of the conjunctivæ, congestion of the throat, etc. Certain forms of iodic eruption may simulate both small-pox and syphilis; other examples will

be noted in considering the clinical features of the different drug eruptions.

It seems hardly necessary to suggest to the practised physician that, when cutaneous symptoms appear which present points of dissimilarity with the clinical features of ordinary eruptions, he should make careful inquiry as to what drugs the patient has been taking.

The elements upon which a diagnosis is based relate, not only to the characters of the eruptive form, but its sudden development, usually without fever or severe constitutional disturbance, its distribution, and its rapid disappearance upon cessation of the action of the exciting cause. As before intimated, the prompt return to a normal state of the skin, so soon as the offending drug is withheld, constitutes the distinctive differential sign of drug eruptions.

The offending agent may occasionally be revealed by its presence in the physiological secretions. As most drugs are usually eliminated by the kidneys, and a few in part by the salivary and sweat glands, the presence of the drug may be detected in the urine, sweat, or saliva.

The most approved tests for the detection of the offending agent in the urine will be considered in connection with each particular drug. Many of the recorded tests are applicable only when the drug has been taken in toxic doses, or when its use has been long continued, leading, presumably, to a considerable accumulation in the system. But it must be borne in mind that in many cases eruptive disturbances of the skin are occasioned by small or indifferent doses. For the detection of such minute quantities, the rough tests generally recommended are altogether inadequate, and processes much more refined and delicate must be employed, otherwise the examination of the urine

would lead to results which are only misleading and deceptive.

Many drugs undergo such marked modifications in the economy, in the process of absorption and elimination, that their morphological identity is entirely destroyed, and, obviously enough, no satisfactory tests can be given for their detection in the excretions.

The sense of smell is often alone sufficient to detect the presence of turpentine and other essential oils in the urine without resort to troublesome tests.

Again, the peculiar and characteristic odor exhaled by the patient who has been taking certain drugs, such as the balsamics, may afford convincing proof of the nature of the exciting cause.

The grayish-brown discoloration of the skin from the prolonged use of arsenic, the slaty-gray pigmentation caused by nitrate of silver, could hardly be mistaken.

There are many other important diagnostic distinctions to be drawn from the character of the eruption as a whole —its configuration, grouping, the parts affected, its course, etc., which are of much more significance than the elementary lesions.

It is important to bear in mind, however, that in many cases the clinical features of drug eruptions have nothing distinctive, nothing definite, nothing fixed. They are as varied in their manifestations as are the physiological peculiarities of the individual in whom they develop; neither in their mode of invasion, their eruptive elements, nor in their subjective symptoms can they be distinguished from eruptions of constitutional origin.

TREATMENT—PROPHYLAXIS.

In the immense majority of cases of eruptions, caused by either the external or internal use of drugs, the treatment is simple and promptly efficacious. Suppress the cause, the accidents will cease to appear. In exceptional cases, the effect on the skin in the shape of new lesions, still continues to be manifested for a short time after the discontinuance of the drug, depending, possibly, upon interference with its elimination by the usual channels, and its longer retention in the system. Again, the morbid impress upon the skin may be perpetuated by a diathetic condition, and in the severer forms by some general cachexia, or local debility of the cutaneous tissues, which retards the prompt return to a normal condition.

But, in general, it may be said that, no matter how marked the cachexia or how grave the systemic complications present, the eruption begins to improve upon cessation of the use of the drug. As before intimated, this tendency to spontaneous recovery is a constant and invariable feature of drug eruptions, and constitutes an important differential sign, which distinguishes them from skin affections of constitutional origin.

In certain cases, in which the requirements of the patient's condition may demand a continuance of the use of the drug, notwithstanding its irritating effect upon the skin, the expedient of diminishing or increasing the dose does not apparently modify its untoward effects. In a majority of cases, patients who manifest this idiosyncratic intolerance cannot take the drug in *any* dose without this coincident liability to eruptive disturbance. It has been claimed, however, that the irritating influence of many

drugs may be counteracted or held in abeyance by a combination with certain other drugs which act as corrigents, suppressing the cutaneous irritation without defeating the therapeutic object in view. For example, hydrobromic acid is said to counteract the untoward effects of quinine.

Arsenic given in combination with iodide of potassium will, it is claimed, prevent the characteristic acneiform eruption. Sulphide of calcium, belladonna, sulphaniline, etc., are said to exert a similar corrective action. Many other expedients for counteracting the morbid determination of drug action towards the skin will be considered in connection with the study of particular drugs.

It must be confessed, however, that these assertions rest upon a very slender support of clinical observation, and must be regarded in the main as *post hoc* conclusions.

It may be accepted as a fact, definitely demonstrated by clinical experience, that medicines which stimulate the functional activity of the kidneys, thus increasing their eliminating capacity, exert a marked modifying influence upon the tendency of many drugs to cause cutaneous irritation. The administration of iodide of potassium in large quantities of Vichy, soda-water, milk, or other diluents is to be recommended on this account.

The free use of diuretics will be found serviceable in abating the intensity, and hastening the involution of many eruptions caused by the internal use of drugs.

Unna has lately recommended as a prophylactic measure against the toxic effects of pyrogallol, chrysarobin, sulphur, and other reducing agents the free use of mineral acids, with the view of diminishing the alkalinity of the blood. He prescribes during the administration of these drugs dilute hydrochloric acid, fifteen to thirty drops a day. Should toxic symptoms develop, the dose is in-

creased to five to ten grams a day. He has never observed bad results from this method.

The local treatment of drug eruptions will vary according to the degree of inflammation present, the extent and severity of the lesions, and the intensity of the subjective symptoms.

Persons whose occupation brings them in contact with irritating substances, as workmen employed in drug manufactories, should change their vocation, or else use measures to thoroughly protect the exposed parts.

The treatment of the simpler forms of drug dermatitis should be essentially palliative; soothing and protective measures should be alone employed. For the relief of the distressing sensations of burning and itching, which are so often a prominent feature, the use of hot baths, medicated with soda or borax, followed by the free dusting of the surface with an inert powder, will be found beneficial. For this purpose, powdered talc, lycopodium, Fuller's earth, or the following: Pulv. zinci, ʒ ij.; Pulv. camphoræ, ʒ ss.; Pulv. amyli, ʒ v. M.—are as good as any. A Turkish bath, when available, constitutes the most promptly efficacious means we possess for the relief of pruritus. The use of antipruritics in the form of a spray, as carbolic acid, ʒ ij.–iv.; glycerin, ℥ ss. to water 1 pint, painting the surface with a solution of cocaine (2 per cent), or of menthol (grs. ij.–x. to the ounce); lotions of lead and opium, the black wash, grindelia robusta (ʒ i.–ij. to ℥ iv. of water) etc., are recommended. Bland ointments, as ung. zinci benzoati, ung. diachyli, or an ointment of oleate of bismuth prepared after the following formula: Bismuthi ox., ʒ i.; Acidi oleici, ʒ vij.; Ceræ alb., ʒ iij.; Vaselini, ʒ ix.; Ol. rosæ., gtt. ij. M.; or, when the skin is not broken an ointment of chloral and camphor (āā ʒ ss.–ʒ i. to ℥ i. of vaseline) may be employed.

In the treatment of the severer forms of pustular and ulcerative lesions, the use of powdered iodoform or dressings of carbolized vaseline will be found to hasten the reparative process.

In the treatment of furuncular lesions, the continuous application of camphorated oil is serviceable in relieving pain and promoting resolution.

ACIDUM BENZOICUM—SODII BENZOAS.

Friar's balsam, which is but another form of the comp. tincture of benzoin, is credited with the production of eruptive phenomena. Fox reports a case of a very extensive eruption of purpura urticans in a patient who had been directed to inhale the vapor of Friar's balsam two or three times a day. The eruption was confluent upon the trunk, more discrete and urticaria-like upon the extremities. Fox says that the rash may result from reflex disturbance or from the presence of the drug in the cutaneous capillaries—the latter he thinks probable from the strong odor of the drug exhaled.

Benzoic acid, upon the presence of which the virtues of the balsam chiefly depend, is irritant to both cutaneous and mucous surfaces.

Vanini observed in a patient, for whom he had ordered small doses of benzoic acid, a maculo-papular eruption develop on the fourth day. The skin of the trunk became covered with an eruption composed in part of somewhat pale, rose-colored macules of irregular form and extent, and in part of bright-red papules, from the size of a poppy-seed to that of a grain of millet. In some places, the papules were distinctly discrete, while in others they were notably confluent, giving to the skin a uniform, raised

aspect. Around the papules and the erythematous spots, the skin presented a normal color.

The following day, under continued use of the drug, the eruption extended to the face, neck, upper and lower extremities; only the surface of the thighs remained free. The use of the medicine was now suspended, and on the fourth day the macules had faded, the papular element disappearing in about ten days without treatment.

Rohe reports two cases in which the internal use of benzoate of soda in medicinal doses caused eruptive disturbance. The rash was erythematous, with well-defined borders, and was attended with considerable itching. The eruption disappeared, with slight desquamation, upon discontinuance of the drug. It was redeveloped several times by a repetition of the use of the drug.

ACIDUM BORACICUM—SODII BORAS.

According to Stillé, the long-continued use of borax sometimes produces an impetiginous eruption of the skin.

Modadewko reports two cases, in which a five-per-cent solution of boracic acid, used for washing out the pleural cavity, occasioned an erythematous rash over the face, trunk, and extremities.

Bruzelius saw a wide-spread erythema make its appearance after a few days' use of a four-per-cent solution of boracic acid taken as an injection in chronic diarrhœa. The eruption was confluent about the neck, and well developed over the body.

Gowers reports three cases, in which borax administered for a long period to epileptics determined an eruption perfectly characetristic of psoriasis. Scaly patches of variable dimensions, some of them three-quarters of a centimetre in diameter, occupied the trunk and limbs,

especially the upper extremities, and were spread over both extensor and flexor surfaces; the face was not invaded. The aspect of the eruption was quite characteristic of psoriasis, although there was less thickness of the scales than in spontaneous psoriasis. In two of the cases, the addition of a small quantity of arsenic to the borax caused the rapid disappearance of the eruption.

Johnson reports a case in which the injection of 3.6 grams of boric acid was followed by headache, fever, injection of the conjunctivæ, and the appearance of an eruption consisting of a bright erythematous redness, papules, and bullæ. The eruption was localized on the extensor surfaces of the limbs and around the articulations, and disappeared within four days. The acid was readily detected in the urine. In a number of experiments with the application of boric acid in the form of an ointment to the skin, the urine became promptly charged with the borate.

Tests for Boric Acid and Borax.

When notable quantities of boric acid or borax are present in the urine, they may be detected by evaporating the urine, previously rendered alkaline by soda, to a small bulk, then acidulating (slightly) with hydrochloric acid, and dipping into it one-half of a strip of turmeric paper; the latter, when dried upon a watch-glass at 212° F., will exhibit a peculiar red color upon the immersed portion. If this is then moistened with a solution of a caustic alkali or alkali carbonate, the color changes to bluish-black or greenish-black. But a little dilute hydrochloric acid immediately restores the previous tint.

If the urine is rendered alkaline by soda, then evaporated to a syrup, the latter mixed with a proper quantity of pure white sand and then evaporated to dryness, the

residue powdered, covered with alcohol, and concentrated sulphuric acid added, on igniting the alcohol, this will burn with a green, or green-bordered flame.

ACIDUM CARBOLICUM.

The irritating effect of carbolic acid directly applied to the skin varies from a slight erythema to complete destruction of the tissues, depending upon the strength of the preparation used and the duration of its contact. The application of strong carbolic acid to the skin causes a painful burning sensation, less pronounced, however, than in the case of other caustics; the affected tissues become white, their vitality is destroyed, and a slough is formed.

Abundant opportunity has been afforded for the study of the effects of weak solutions of this agent upon the skin by the general employment of carbolized dressings in the antiseptic treatment of wounds. The most common eruptive form is an erythema which is especially manifest upon regions where the skin is fine and delicate. The inflammatory reaction may result in the formation of vesicles resembling eczema. Strong solutions of carbolic acid may cause gangrene of the skin, which is usually limited to the region of application.

The use of this agent in the form of a spray no doubt facilitates its rapid absorption through the skin by the minute subdivision of the particles. Irritation of the skin may appear on parts not subjected to the action of the spray from absorption.

Similar effects may follow the introduction of carbolized preparations in abscesses and in cavities lined with mucous membrane, as the vagina and rectum.

The cutaneous effects of carbolic-acid poisoning are usually accompanied with nausea, headache, vomiting, and

diminution in the quality of urine voided. The urine becomes of a dark olive color.

Koster-Syke reports a remarkable idiosyncrasy against carbolic acid in his own person ; and his susceptibility was so marked that merely handling a vessel containing carbolic acid sufficed to develop the outbreak of an eczematous eruption.

Zeissl reports a case of erythema urticatum following the application of Lister's bandage. The eruption appeared upon the back, sides, and extremities in the form of an erythematous redness, studded with artificial wheals. The eruption subsided when the carbolic-acid dressing was withdrawn.

Browne reports two cases of carbolic rash under his care resulting from antiseptic dressings. The eruption was of a bright scarlet, which commenced about the edges of the wound, spread over the contiguous surfaces, and became generalized. The eruption was followed by desquamation and some albumin in the urine, resembling in many particulars scarlatina, for which it was at first mistaken.

Dreyfuss observed, as the result of phenic-acid dressings to the wounds caused by circumcision in two Jewish infants, a generalized erythematous eruption, accompanied with abundant perspiration and hyperthermia. There was also a tendency to the formation of furuncles lasting several weeks thereafter.

In a case of poisoning from drinking impure carbolic acid treated by Penasse, he observed in conjunction with other toxic symptoms an eruption, preceded by violent itching, papular in character, situated upon the arms and anterior superior region of the trunk.

Rose reports the occurrence of gangrene of the finger from the application of a strong carbolized cotton dress-

ing. This result may possibly have been due to interference with the circulation from compression, as similar results have been observed from simple collodion dressings to the fingers.

Tests for Carbolic Acid.

Normal urine contains small quantities of phenol-sulphuric acid, which does not readily respond to reagents until it has been split up into free phenol and sulphuric acid by boiling the urine with hydrochloric acid.

Urine containing notable quantities of carbolic acid has often a dark color, particularly when the drug has been absorbed from external application.

It may be detected in the following manner:

1. Place into a test-tube about two grains of chlorate of potassium, pour upon it about one-half fluidrachm of hydrochloric acid, and allow the reaction to proceed for about one minute. Then dilute with about three fluidrachms of the urine. Now carefully pour down, along the inner side of the test-tube, a little water of ammonia, so that this will form a layer on the liquid contained in the test-tube. If any carbolic acid is present, there will be a colored ring—varying from faint rose-red to dark-brown—at the line of contact of the two liquids.

2. Or, mix the urine with one-fourth its volume of water of ammonia, then add a little solution of chloride of lime (1 in 20), and warm gently. A fine blue color, more or less deep, will make its appearance.

The *treatment* consists in suppression of the exciting cause. When the cutaneous effects of the drug are accompanied with symptoms of general phenic intoxication, diuretics should be given to hasten the elimination of the drug. Sulphate of soda internally, as recommended by Baumann and Sonnersburg, injections of atropine and

vigorous frictions are probably the best measures for overcoming the toxic effects.

ACIDUM CHRYSOPHANICUM. CHRYSAROBIN.

Araroba or Goa powder, from which chrysarobin is principally derived, is extremely irritating to the skin and mucous surfaces. Workmen employed in cutting up and pounding the wood from which the powder is obtained are compelled to protect their hands, eyes, and throat against the irritating dust.

The application of chrysophanic acid to the skin causes an irritation which varies with the strength of the application and the susceptibility of the patient. The effect of the irritation is by no means limited to the seat of application, as in the case of most external irritants, but may extend over a considerable contiguous surface, or may leap to a cutaneous area some distance removed. Chrysophanic conjunctivitis not infrequently follows the application of this agent in the treatment of parasitic diseases of the scalp.

The following forms of inflammatory disturbance may be described :

1. *A Hyperæmia with a Peculiar Purplish or Prune-Juice Discoloration of the Skin*, which is quite persistent.

2. *An Erythematous Eruption.*—This may appear as a slight erythematous halo around the points of application, or the congestive redness may become intensified with tumefaction of the tissues, and take on the characters of a general dermatitis. It usually disappears with a slight desquamation.

3. *A Papular Eruption.*—The inflammation may manifest itself as pin-head-sized, reddish-brown, firm papules, some of which may become vesicular and pustular; according to Kaposi, who first described this eruptive form, they correspond to the openings of the follicles. This drug has

also the property of irritating the sebaceous glands, producing a chrysarobin acne, with a tendency to the formation of nodules, rather than of papules or pustules. As in tar acne, each lesion has a black point in the centre.

Farquharson reports a case in which the application of an ointment of chrysophanic acid to a patch of tinea tonsurans caused a dusky-red condition of the entire scalp. From the scalp the inflammation extended to the face which was covered with very minute papules, thickly studded over perfectly normal skin, and attended with a good deal of itching. The eruption disappeared on leaving off the ointment.

4. *A Pustular and Furuncular Eruption.*—This form of eruption is by no means uncommon. The pustules and furuncles are hard and painful, and suppurate slowly. I have reported a case of tinea barbæ coming under my care in which the application of an ointment (twenty grains to the ounce) produced a number of large inflammatory nodules, with much infiltration and congestion, resulting in a hard, brawny condition of the sides of the face and neck, and which persisted for two or three weeks. Brocq observed a man dying at the St. Louis Hospital, with the most intense general erythema accompanied by symptoms of severe poisoning from chrysophanic acid. He also saw, in the service of M. Vidal, a case of general exfoliative dermatitis, of two months' duration, which had been occasioned in the same way.

An erysipelatous condition has been observed in connection with the use of this drug. It most usually affects the head and face with considerable swelling and puffiness of the tissues, sometimes leading to closure of the eyes. The genitals, as well as the face, are specially liable to the irritant action of the drug. It would seem that these irritating effects depend less upon the strength of the prepa-

ration than upon the susceptibility of the skin of the individual to irritant action. In a number of cases which have come under my observation, an intense dermatitis has been developed by the use of a comparatively mild ointment (5 grs. to ℥ i.). In two of these cases, there was exfoliation of the epidermis in large flakes, as in exfoliative dermatitis. These irritant effects from mild applications are specially liable to occur in women and children, particularly blondes with fine, delicate skins, and render the employment of the agent in any strength impossible.

Tests for Chrysarobin and Chrysophanic Acid.

Chrysarobin appears in the urine either as such or as chrysophanic acid.

It may be detected by adding to the urine—concentrated, if necessary— a little caustic potassa. If this produces a reddish or red tint, chrysophanic acid is present. If the tint is rendered deeper by blowing air through the liquid, or if it only makes its appearance after the passage of a current of air, chrysarobin was present. It is only when this has been converted into chrysophanic acid by contact with air, in solution, that the color is developed.

ACIDUM NITRICUM.

According to Stillé, a fine pustular eruption sometimes appears upon the skin after the internal use of nitric acid in medicinal doses.

Bazin found, after two or three frictions with a dilution of nitric acid, that the skin presented a diffuse redness, over which were scattered small, solid elevations; after the fourth friction, these little elevations became pustules, which soon gave place to small ulcerations, extremely superficial, presenting a blackish point at the centre, and a whitish zone of pseudo-membranous aspect at the per-

iphery, which was surrounded by an inflammatory areola. As the eruption disappeared, small epidermic scales were seen disseminated over the patches.

ACIDUM PYROGALLICUM. PYROGALLOL.

The topical application of pyrogallic acid may occasion irritation of the skin of varying degrees of severity, from a slight dermatitis to a destruction of the skin, followed by ulceration and sloughing. According to Jarisch, who first introduced the drug to the notice of the profession, it excites localized inflammation which may lead to epidermic desquamation and the formation of vesicles. This is specially liable to occur on the extremities.

Its most common and characteristic incidental effect upon the skin is, according to Besnier, the production of an erythemato-vesicular eruption.

Allen reports two cases in which a ten-per-cent ointment of pyrogallic acid produced a blackened and charred condition of the skin for an inch or more beyond the area of the application, with a dermatitis of the adjacent surface. In one case, the charred tissues sloughed off, leaving an ulcerated surface, which slowly healed, succeeded by a disfiguring cicatrix.

Tests for Pyrogallic Acid.

When this acid has been absorbed, the urine generally appears dark-colored, varying from brownish to near black.

When the urine is not loaded with coloring matters, pyrogallic acid may be recognized by its behavior with iron salts, giving a deep-blue color with ferrous sulphate, and a brownish-red with ferric chloride. These tints are, however, comparatively faint when only traces are present, and the blue tint, particularly, will be modified to a sort of muddy

green. Additional proof may be obtained by shaking another portion of the urine, rendered alkaline with caustic potassa for some time in a test-tube. If it becomes darker in tint, pyrogallic acid may be assumed to be present. Or, a little hot nitric acid may be allowed to react with a piece of starch in a test-tube, and a few drops of the nitrous acid thereby produced added to the urine, which will be rendered brown, if pyrogallic acid was present.

The irritant effects of pyrogallic acid upon the cutaneous surface are often accompanied with symptoms of general poisoning.

In the treatment of the toxic effects of pyrogallic acid, Besnier recommends the inhalation of oxygen and the subcutaneous injections of ether. Unna has suggested the administration of dilute hydrochloric acid as a prophylactic measure.

ACIDUM SALICYLICUM. SODII SALICYLAS.

Irritation of the cutaneous surface has been frequently observed after both the external and internal use of salicylic acid. Its substitution for carbolic acid as an antiseptic in the treatment of wounds has shown that it is even more irritating than the former agent. Callender has stated that a two-per-cent solution tends not only to irritate the wounds, but to bring out irritable vesicles in their neighborhood. He observed that an ointment of salicylic acid, one part to twenty, brought out a vesicular eruption, the vesicles containing a clear fluid, the intervening skin much inflamed. The area affected was limited to the surface covered by the dressing. Sir Wm. Jenner records a case where the application of salicylic acid to a burn developed a rash very like that of scarlet fever.

Various forms of eruptive disturbance, erythematous, urticarial, vesicular, petechial, etc., have been observed

from the internal use both of salicylic acid and salicylate of sodium.

Farquharson reports a case where the use of the drug produced a peculiar bright, punctate rash with erythematous patches, eventually surmounted by vesicles, accompanied with sore throat and constitutional disturbance suggestive of scarlatina.

Erb observed after several days' use of seven-and-a-half-grain doses of salicylate of sodium, an eruption which was at first regarded as an anomalous form of scarlatina. Upon the face, neck, and body it showed itself as a bright red, confluent exanthem. Upon the arms and legs the redness was more blotchy, without papular elevations. The conjunctiva and mucous surfaces of the throat were intensely reddened. The eruption disappeared within two days after cessation of the drug. Three weeks later, a similar eruption was developed by three seven-and-a-half-grain doses of salicylic acid.

Dreschfield observed in the case of a lady an erythematous eruption which was repeatedly developed by the internal use of salicylate of soda. The whole body became covered with an erythematous rash. The face, arms, and legs were very œdematous, and the lips very much swollen. Upon examination of the urine with perchloride of iron, a distinct salicylic acid reaction was obtained. Within a few days, the rash and œdema disappeared, and the skin peeled off from the face, legs, and arms in thin flakes. Another patient, suffering from acute articular rheumatism, for which he was ordered fifteen-grain doses of salicylate of sodium three times a day, was soon troubled with a well-marked urticaria. A second attack of urticaria was promptly developed upon resuming the use of the drug. He also reports a case of skin eruption very closely resembling erythema nodosum, following the use of a vaginal

wash containing salicylic acid. On a previous occasion, salicylate of sodium, taken internally by the same patient, had produced an eruption of similar character.

Parsons saw in the case of a lady who was taking small doses of salicylate of soda a rash resembling measles upon the face, hands, arms, and body. The rash disappeared upon discontinuance of the drug, and reappeared when its use was resumed.

Heinlein observed from the use of four ʒ i. doses of salicylate of sodium a diffuse redness of the left half of the face, the lower extremities, and the right side of the chest, with slight œdema of both eyelids, the upper lip, and the legs as far as the middle of the thighs. These symptoms promptly disappeared with the cessation of the medicine. After a remission of several days, a drachm dose was administered; half an hour afterward there appeared a diffuse erythematous redness over the greater portion of the body, while a profuse eruption of wheals was observed over the abdomen and lower extremities, with considerable œdema of the face. The urticarial phenomena disappeared in the course of an hour or two, the erythema by the next day.

Leube also saw an eruption of urticarial wheals follow the use of a drachm dose of salicylate of sodium.

Wheeler reports a case where the drug produced an eruption of vesicles and pustules upon both upper and lower extremities, accompanied with profuse perspiration. It disappeared on stopping the medicine.

Rathery says: "every time I have occasion to use salicylate of sodium in my own person, my hands and body are covered with a pemphigoid eruption."

Cavafy reports a peculiar eruption from the use of salicylate of sodium. It consisted of erythematous patches which became covered with vesicles, some very minute,

others larger and confluent, while others were grouped, resembling herpes.

Freudenberg saw, after five-grain doses of salicylic acid taken daily for five days, a petechial eruption in which some of the petechiæ were as large as a half-dollar, other extravasations occurred in the shape of vibices. They first appeared on the back, but spread the following day over breast, arms, shoulders, hips, and thighs. The spots became pale in the course of a week, and the epidermis was exfoliated in great scales from the affected parts. Second experiment in the same patient produced a similar result.

Rosenberg observed an eruption of purplish spots all over the body of a patient from the use of salicylic acid. The medicine was discontinued, but upon another trial a month later, in addition to the purpuric eruption, there appeared a number of blebs filled with serum, situated on the back and extremities, and also upon the conjunctiva and mucous membrane of the tongue and lower lips. A third trial of the medicine resulted in a precisely similar eruption.

Watelet reports two cases of rheumatism treated with salicylic acid, in which the drug occasioned coldness of the extremities, and in one case gangrene of the lower extremities.

The erythematous eruption produced by salicylic acid and its salts bears a striking resemblance to that of antipyrine, belladonna, chloral, etc. The rise of temperature, sweating, œdema, with which the erythema is usually accompanied, are undoubtedly vaso-motor phenomena. Experiments upon animals have shown that the salicylates act primarily and principally upon the vaso-motor centres.

Tests for Salicylic Acid and Salicylates.

On adding to the urine a little solution of ferric chloride, there will, at first, appear a flocculent precipitate of phosphate of iron; but on further addition of the reagent, the liquid will assume a more or less intense violet color.

If there is doubt, concentrate the urine to a small bulk, acidulate it with hydrochloric acid, then shake it with a mixture of equal parts of chloroform and ether. Evaporate the latter, after separation, and apply the above test to the residue.

ACIDUM TANNICUM.

It is well known that tannic acid exerts an influence upon the functions of the skin, notably diminishing the insensible perspiration.

The sole reference which I have found in medical literature relating to the irritant effects of tannic acid upon the skin is that of Dr. Williamson. He records the case of a lady in whom an erythematous eruption, affecting the face and neck, was developed three separate times by the use of tannic acid. Tannin injected into the rectum, tannin accidentally inhaled, the ingestion of an infusion of uva ursi leaves, which contain 35 per cent of tannin, were all followed by identical symptoms. An interesting fact in this connection was, that gallic acid, taken internally, produced no untoward symptoms.

Gallic acid passes off through the kidneys unchanged within one hour after its ingestion. Tannic acid is converted into gallic or pyrogallic acid before excretion.

ACONITUM.

This drug, as is well known, exerts a marked influence upon the cutaneous system.

The external application of aconite to the skin causes first a sensation of tingling and then numbness, from the paralyzing action of the drug upon the sensory nerves. Congestion, redness, and an eruption of itchy vesicles have also been observed, and according to Dierbach, quoted by Piffard, it may produce an erysipelatous inflammation.

Many writers on materia medica speak of an irritable vesicular eruption, which frequently follows the internal use of aconite. It is attended with a sense of formication and excessive itching. Pustules and blebs have also been observed.

AMYGDALA AMARA.

Phillips says that an eruption resembling urticaria often comes out on the skin after the ingestion of this drug.

Gregory noticed such an eruption upon himself after eating a bitter almond. The same effects may follow the use of bitter almond and cherry-laurel water, depending no doubt upon the hydrocyanic acid present in both preparations.

Rayer oberved from the use of frictions with *l'huile de laurier-cerise* an extensive patch of erythema over the loins, nine by six inches in extent. The exanthem consisted of a large non-elevated, red patch, the redness not uniform, the skin appearing as if spotted and discolored at certain points. The red spots gradually became paler, followed by desquamation on the seventh day.

ANACARDIUM.

The oil of the cashew nut is extremely irritant when applied to the skin, producing dermatitis and erysipelas. The effect is not limited to the parts with which it comes in direct contact; extensive inflammatory disturbance

being observed upon parts distant from the point of application. Œdema and eczematous inflammation of the face have been observed.

Stickney noted from its local application, pain, itching, red papules changing to pustules, crusts, and desquamation.

According to Bazin, the oil, when applied to the skin, sometimes produces vesicles which rapidly become purulent.

Schwerin reports a case of a woman who had put one-half of a bean in her ear to relieve toothache and pain in the face. A violent erysipelas resulted. The face was bloated, both eyelids infiltrated, and the ear, cheek, and front of the neck reddened and swollen. The external auditory canal, the external ear, and the adjacent surfaces were covered with vesicles.

In another case, also quoted by Lewin, an anacardium bean, divided longitudinally, was placed upon a string hung around the neck in such a manner that it lay over the manubrium sterni. Two days later, an erysipelas had developed, extending over the whole front of the chest, the mammæ, the region of the shoulder as far up as the lower jaw, and presenting a number of vesicles upon its surface.

Hughes states that, taken internally, anacardium has a remarkable influence upon the skin. In its slightest degree of action, it causes the appearance of wheals like those of urticaria tuberosa, with itching, burning, and swelling, terminating in desquamation. When operating more intensely, it develops eczematous vesicles, and even bullæ.

It is claimed that the irritating effects, which are so often observed from the use of preparations of vanilla, are due to the oil of cashew, with which the vanilla pods are coated before being sent to market.

ANTIMONIUM. ANTIMONII ET POTASSII TARTRAS.

The external application of tartarized antimony to the skin excites a very characteristic eruption which, in its course and the anatomical form of its lesions, resembles the eruption of variola. Its contact produces a hyperæmia, then papules which are converted into vesicles, which, later, develop into pustules. The pustules mature about the fifth day, desiccate and form scabs, which often leave, on falling, indelible cicatrices. Sometimes it produces large ecthymatous ulcers, with deep sloughs and extensive loss of tissue resulting in permanent disfiguration. Jacobi, of Wurzburg, reports a case in which there was destruction of the bony tissue, the application of antimonial ointment to the scalp causing a perforation of both tables of the parietal bone. Applied on distant parts of the body, it may cause eruptions on the genitals or around the anus, without direct contact. Pustular eruptions not infrequently develop secondarily on the genital parts several days after inunction with tartarized antimony, without there having been, so far as could be ascertained, a transference of the drug to these parts from the original point of application. This would seem to be due to the absorption of the drug and its presence in the circulation.

Opinion is divided as to whether the effects are due to the irritant action of the drug upon the peripheral nerves leading to inflammatory changes, or to a direct action upon the coats of the vessels themselves from the presence of the drug in the vascular channels.

Trousseau says that the internal administration of tartarized antimony will produce a vesiculo-pustular eruption, like that produced by the salt applied to the skin.

Imbert Gourbeyre cites five cases in which eruptions

closely resembling those produced by tartar emetic ointment have appeared during the internal administration of the drug. He also quotes a case where a red eruption occurred over the whole body from a single large dose of antimony. This observation has been duplicated in the experience of others. In other cases, urticarial and pustular eruptions have been observed from the internal use of antimony.

Langston states that, after the administration of tartar emetic for three or four days to his wife, an eruption, consisting of a dense crop of tartar emetic pustules, broke out all over the surface of the upper part of the body, including the arms. The outbreak of the eruption was preceded by an alarming sensation of numbness and tingling.

Tests for Antimony and Arsenic.

Among the various methods available for their detection, the following will probably be the most expeditious in the hands of the physician:

Acidulate the urine strongly with hydrochloric acid, in a narrow-mouthed flask, immerse in it a piece of *bright* copper wire or foil, and boil for some time. If, after the urine has boiled down to one-half, there is no visible metallic deposit upon the copper, the above two metals may be regarded as absent. If a metallic coating has been produced, this is to be examined as stated below.

Should the urine contain constituents which are coagulated or precipitated by boiling or acidification, they must first be removed.

The coated copper wire or foil is taken out of the flask, washed thoroughly in water, dried, and then heated in a glass tube closed at one end, the further procedure being that laid down in all text-books.

ANTIPYRINE.

Although the introduction of antipyrine as a remedial agent is of comparatively recent date, yet a large number of cases have been reported in which eruptive disturbances have followed its employment.

The eruption of antipyrine is usually erythematous in character. It consists of small, irregularly circular, slightly elevated reddish patches, which may be discrete, or confluent forming large patches resembling the exanthem of rubeola. The redness disappears on pressure, leaving a brownish pigmentation. The duration of the eruption is rarely more than five days; it is occasionally followed by desquamation. It is frequently attended with profuse sweating, and causes more or less itching. Its seat of predilection is the chest, abdomen, and back, but it may also occur upon the extremities; it affects the extensor rather than the flexor surfaces. The face and upper part of the neck are usually spared. The eruption may exceptionally follow a small single dose of the drug but, ordinarily, it is only provoked by a continuous course of antipyrine treatment for several days, although in a large number of cases experimented upon, the eruption did not occur in the exact period during which the largest quantity of the drug was taken. It begins to subside promptly on the disuse of the drug, and generally, but not always, recurs when the drug is again administered.

Ernst was the first to note the incidental effects of antipyrine upon the skin. He reports five cases in which an eruption resembling measles was developed upon the trunk and extremities, and also upon the palmar and plantar surfaces.

Leube records a case of a "measly eruption" following

the employment of antipyrine, which promptly disappeared with the cessation of the use of the drug. Its resumption brought out a uniform scarlet-red eruption over the entire surface of the body, attended with swollen eyelids, injected conjunctivæ, and free lachrymation.

Biermer, reported by Alexander, observed in three cases measly eruptions and one case in which the use of the drug was always followed by an urticaria.

Frankenberg observed in seven patients, out of a large number submitted to antipyrine treatment, an eruption of reddish, irregularly round spots, the size of a lentil, giving the skin the appearance of a "rose marbling."

In two cases of antipyrine rash reported by Bloomfield, the eruption consisted of slightly raised erythematous patches, one-eighth to one-half inch in diameter, of an Indian red color, covering the entire body. Here and there were a number of vesicles the size of a No. 6 shot.

Bielschowsky observed, after the use of antipyrine in a case of typhoid fever, an eruption of hemorrhagic wheals on the extremities. They followed the subsidence of the typhoid rash, and were succeeded by a scarlatinoid eruption.

Graham reports the occurrence of a patch of purpuric maculæ on the back of a patient who was ordered five powders of antipyrine, twelve grains each.

Strauss reports a case in which moderate doses produced, in conjunction with severe constitutional effects, a purpura-like eruption on the back and limbs.

Draper treated twenty cases of typhoid fever with antipyrine. In six of these cases, the drug produced an eruption resembling measles, and in one case, in which large doses were continued for a prolonged period (twenty days), the drug caused a copious erythematous rash, which was

followed by an eruption of furuncles. In one case, there was a macular eruption of a purpuric character.

The mode of production of the cutaneous effects of antipyrine is to be explained by the action of the drug upon the vaso-motor system of nerves. It causes paralysis of the vaso-motors which is followed by dilatation of the cutaneous vessels. The largely increased amount of blood present would naturally favor the production of the characteristic erythematous and urticarial eruptions. The hemorrhagic exudations occasionally observed are probably produced in the same way.

Tests for Antipyrine.

Antipyrine may be volatilized when distilled with water. Urine, however, after small doses of antipyrine, does not yield the latter by distillation until after it has been boiled with hydrochloric acid, which fact permits the conclusion that antipyrine is, at least partly, eliminated as a copulated compound, probably as antipyrine-sulphuric acid. When much antipyrine has been taken, however, it is found free (probably only in part free) in the urine.

Urine containing free antipyrine, or in which it has been set free by boiling with a little hydrochloric acid (in which latter case the excess of acid should be subsequently neutralized) is rendered red by ferric chloride, and bluish-green by nitrite of sodium or by dilute nitrous acid. The latter is best prepared by allowing hot nitric acid to act upon starch, and diluting with a little water.

ARGENTI NITRAS.

The peculiar discoloration of the skin following the prolonged ingestion of nitrate of silver, which has been variously described as "bluish-gray," "steel-gray color," "grayish-black," and which is most marked on the face and flexor surfaces, is comprehended under the general term "argyria." It is caused by a deposition of granules of the metal in the tissues, most abundant, according to Neumann, in the papillary layer. Granules are also found in the other layers of the skin, also on the external wall of the hair follicles, sebaceous glands, and sweat-tubes. I have seen, in the case of a young woman under my care for syphilis, who had previously used for several months a solution of nitrate of silver for the relief of an obstinate granular conjunctivitis, a copious deposit of the metal upon the conjunctival mucous membrane, which had caused a blackish discoloration, quite noticeable even at a distance.

Charcot observed, after the long-continued ingestion of nitrate of silver, an erythematous and papular eruption attended with pruritus.

Argyria derives a certain clinical importance from the fact that it may be mistaken for Addison's disease.

According to Gamberini, the internal administration of iodide of sodium or potassium, and the long-continued use of warm baths, has proved successful in removing the discoloration of the skin caused by nitrate of silver.

ARNICA.

Arnica, which is popularly regarded as a sovereign remedy for contusions, sprains, etc., is often prescribed by the physician under the mistaken impression that, even if it does no good, it can do no harm. Oftentimes, however, the external application of the tincture of arnica, even when largely diluted, is far from proving innocuous and inoffensive.

The strong tincture always exerts a local irritant action when applied to the skin, and in susceptible persons it causes eruptive disturbances of various forms and degrees of severity.

The most common form of arnica dermatitis is an erythemato-vesicular eruption which presents certain analogies with the poison oak eruption. The irritant action of arnica is first manifested by a hyperæmia of the affected surfaces, attended with a sensation of burning and intense itching.

Ordinarily within a few hours, there is developed upon the erythematous base an eruption of pin-head-sized, reddish papules, intensely itchy, and which soon become converted into miliary or pea-sized vesicles, which may remain discrete or form, by their fusion, bullæ of considerable size and irregular outline. The walls of the vesicles are usually ruptured by rubbing and scratching, and the exudation dries, forming yellowish or brownish crusts.

According to White, most cases of arnica dermatitis present a distinctly eczematous type in the development of hyperæmia, papules, vesicles, excoriations, and crusts in regular order, yet many cases have been observed in which the primary, immediate effect was the production of large blebs or blisters.

Exceptionally, the dermatitis may spread over surfaces remote from the region of original application by transference of the irritative agent by scratching or otherwise.

Fox has observed that the tincture of arnica may produce an erythema and tumefaction of the parts to which it is applied, and even a veritable eczema.

Wilson reports a well-marked eczematous eruption from application of tinct. of arnica to a contused shoulder. The whole of the front of the shoulder was of a deep red color, and presented the character of an eczema vesiculosum et ichorosum, and extending over the whole of the right side of the chest was a crop of pimples of eczema papulosum seu leichenodes, the pimples being large and of a dull red color; same eruption on thighs, scrotum, head, face, and hands. He refers to numerous cases reported by Prof. Galassi and Mazzoni, of Rome, in which the symptoms of the eruption were slightly elevated red puncta, which are quickly converted into middle-sized vesicles similar to those produced by croton oil, swelling and burning heat, and spreading to surrounding parts.

Violent erysipelatous inflammation, even ending in death, has resulted from the application of arnica. Purpuric eruptions have also been recorded.

Farquharson reports a case occurring in Hebra's clinic, in which an acute inflammation of both hands, with huge blisters almost running into gangrene and causing partial destruction of the tissues, was caused by the application of the tincture of arnica. He also records a case coming under his observation in which a weak solution of tinct. arnica caused an erysipelatous inflammation which slowly spread over the entire body.

Leissus reports two cases in which tincture of arnica applied for contusions produced well-marked symptoms of

vesicular erysipelas; both patients were females with fine, sensitive skins.

Paul de Molènes reports four cases, coming under his personal observation, in which compresses of tincture of arnica applied to contusions caused vesicular and phlyctenular eruptions.

Cartier reports, as a result of the application of tincture of arnica to the face for contusion, an erysipelatous swelling, the face became enormously swollen, closing the eyes; skin bright red and covered with phlyctenulæ, which discharged abundantly a clear lemon-colored fluid; the redness extended to the neck which was occupied by small vesicles; the submaxillary glands were swollen, producing dysphagia; temperature increased, urine scanty, mahogany color, like thatof an icterus patient; although redness and inflammation disappeared under liniment of lime-water and oil, desquamation was not completed for two weeks afterward.

Hendrix reports two cases of erysipelatous eruption from application of tincture of arnica. In one case, the skin was everywhere œdematous, and the eruption covered the whole body and extremities. The entire abdomen was covered with a continuous blister, serum exuded freely from the whole abdominal surface, saturating cloth after cloth.

Paul Cagny states that the tincture of arnica has the same intensely irritating action upon the integument of the horse as in man. He reports a case in which arnica was applied to a bruise caused by the kick of another horse. The parts became hot, swollen, and excessively painful, and presented a blistered appearance. Such results, he observes, are of common occurrence from the use of this application in veterinary surgery.

The internal use of arnica is often followed by diaphore-

sis, erythema, and a sense of pricking and formication of the skin.

Phillips asserts that the irritating effects observed from arnica never follow the use of an aqueous solution, which contains none of the arnicine or volatile oil.

Piffard has suggested that the irritant properties of preparations of arnica flowers may be due to the presence of an insect, the Atherix maculatus, and recommends that preparations made from the root should always be used.

ARSENICUM.

The cutaneous eruptions which follow the external and internal use of arsenic are similar in character. While the external contact of arsenic produces certain changes in the skin which can in no way be distinguished from a dermatitis caused by other local irritants, the severer eruptive forms are probably due to absorption of the drug, and its specific action upon the skin. The irritant effect of the external application of arsenic was known to the writers of antiquity, and has since been studied by numerous observers.

If arsenious acid in a watery solution, or in the form of an ointment or paste, be applied to the healthy skin, there results inflammatory redness, and if the contact be continued sufficiently long, vesicles, pustules, etc., will form, attended with sensations of heat, burning, and pain, precisely as in the application of other vesicants. The hairs on the affected surfaces generally fall out, and there is exfoliation of the epidermis in large flakes. A higher degree of inflammatory disturbance is manifest in the production of erysipelatous swellings, sanguinolent eruptions, and ulcers, attended with toxic effects similar to those consequent upon the internal administration of the drug. Numerous cases are on record where arsenical lotions,

plasters, and pastes have proved fatal. The application of an arsenical ointment (1 to 32) to a cancerous breast covering the space of one and one-half inches, for one night only, caused death from poisoning on the second day. A strong application of arsenic is much safer than a weak one, since the intensity of the inflammation it excites interferes with the action of the absorbents, and the effect remains local.

Abundant opportunities for the study of the changes in the skin caused by external contact have been afforded by the extensive use of arsenic in the form of lotions for the complexion, dusting-powders, etc. A remarkable skin affection which prevailed among infants and children in Brighton in 1818, at first thought to be erysipelas, was traced to the use of a dusting-powder containing fifty per cent of white arsenic. Of twenty-nine attacked, thirteen died. The cases were carefully studied by W. H. Power, and the character of the eruption may be briefly described as follows: In very mild cases, there was erythema and the formation of minute vesicles; in severer cases, blisters and bladders formed in the creases of the skin where the powder was applied; some of the bullæ, when collapsed, left black excavated sores, with indurated and discolored edges. In fatal cases, there was a generally blackened condition of the skin of the groins and pudenda, which quickly became somewhat swollen and hard. A like condition upon the abdomen was occasionally observed about and below the umbilicus, as also the skin of the axilla and folds of the neck. Invasion of these several parts where it occurred, was simultaneous. In some instances, vesication, variously described as "little white blisters," "yellowish bladders," or "bags of water," preceded or appeared about the same time as the blackness. The vesicles breaking discharged clear fluid and left raw, black sur-

faces, which did not, it would seem from the description, take on suppurative or sloughing action. The average duration of the fatal illness was four or five days. The eruption was localized on parts of the body to which the powder was applied.

The various industrial uses of arsenic in the manufacture of artificial flowers, green-colored cards, paper boxes, wall paper, and carpets, fixing dyes, etc., are the prolific source of numerous forms of eruptive disorders. Wood records a large number of cases of poisoning from arsenic contained in wall papers.

It is well known that persons who wear cheap underclothing colored with fuchsine, containing a large percentage of arsenic, or socks died with the same material, are subject to eczematous eruptions on the parts exposed to contact with the coloring matter. Seifert reports the case of a lady who had been wearing stockings colored with an aniline-red containing arsenic. She was suddenly seized with all the symptoms of a gastro-enteritis and an acute hemorrhagic nephritis, besides an eczematous eruption on the dorsal surfaces of both feet. The urine, for some time afterward, contained a small amount of albumin. Impetiginous eczema has been seen on the arms of a lady who wore a bracelet composed of a paste containing a large proportion of arsenite of copper. According to Rollet, who has made a careful study of the cutaneous lesions from the industrial uses of arsenic, erythema is the first degree of arsenical dermatitis. Generally upon the erythema are developed other elementary lesions; papules which enlarge and extend and are covered with small scales of greenish tint, fine, transparent vesicles, and, finally, pustules. These pustules form with conical projections, red at the base, purulent at the summit, and are covered with a small, opaque, yellowish-green crust. If the irritation

continues, the pustules become the points of departure of ulcerations, which progressively increase in breadth and depth. Arsenical eruptions are situated upon parts exposed to contact with the irritating cause, as the face, forearms, hands, interdigital spaces, also the feet and and inguino-scrotal region. The genital parts are peculiarly susceptible to the irritant action of arsenic. Frequently, there are large ulcerations with œdema of the scrotum.

I observed several years ago at the New York Dispensary an eczematous eruption, with deep-seated pustules, on the hands of two young women who were employed in a paper-box manufactory, in which variously colored glazed papers were used.

White reports several cases of arsenical dermatitis, one of intertrigo in an infant, and brown spots resembling pityriasis maculata et circinata of the mother, which were probably due to absorption of arsenical pigments contained in the wall paper, as every other possible factor was eliminated—a theory sustained by the fact that there was immediate improvement upon removal of the patients from the room. Clarke records eczematous eruptions and nasal ulcerations as due to the emanations from arsenical wall papers.

Allen reports having observed several cases of arsenical dermatitis especially marked on the hands, legs, and feet in longshoremen engaged in unloading a cargo of dry hides which had been cured with arsenic. The arsenical dust had sifted through their clothing and low shoes, producing large vesicles and bullæ, followed by ulceration with swelling of the feet, legs, and hands. Papular and erythematous patches, attended with burning and itching, were scattered over the legs and thighs.

Perhaps no drug in the materia medica exerts a more marked influence upon the nutrition of the skin than arse-

nic. Almost all observers have noted its tendency to aggravate eczematous and other acute inflammatory disorders of the skin. Devergie was the first to signalize the fact that cutaneous lesions may be caused by the internal use of arsenic. A most complete and careful study of the arsenical eruptions has been made by Imbert Gourbeyre, and embodied in his admirable monograph upon this subject. According to this authority, the pathogenetic influence of arsenic may be manifested in the form of papular, petechial, urticarial, vesicular, erysipelatous, and pustular eruptions. To these may be added an erythematous or scarlatiniform eruption, the occurrence of which has been attested by numerous observers.

The various preparations of arsenic differ in no sensible degree in their effects upon the skin, so that observations relating to arsenious acid will apply to Fowler's solution, the arsenite of soda, Asiatic pills, etc.

The Erythematous Form.—Although an erythema is the commencing stage of several of the forms of arsenical eruption, it rarely represents the acme or completion of the inflammatory process. Pereira observed in a gouty patient, after taking one-sixth grain of arsenious acid a day, on the third day an intensely red eruption on the face, neck, upper part of the body, and flexor surfaces of the joints, with œdema of the eyelids. The eruption disappeared between the third and fifth days, but desquamation in large flakes continued for nearly two months.

Macnab has observed a rubeola-like exanthem in patients who had taken small doses of arsenic, three-drop doses of Fowler's solution daily for three weeks.

Hyde saw in a young woman who had taken only three medicinal doses of Fowler's solution, a light-red scarlatiniform blush, with a few isolated vesicles, covering both shoulders, the eruption being present, but less distinct, on

the hands and face. Piffard gives numerous references of erythematous and rubeoloid eruptions consecutive to the internal administration of arsenic.

The Papular Form.—According to Imbert Gourbeyre, the papular form occurs as discrete, pin-head-sized papules, first in scattered groups, which unite later to form lenticular papules, occasionally large disseminated patches, which sometimes resemble a papulo-syphiloderm, although of a less coppery hue. The parts affected by preference are the face, neck, hands, and genital organs. The eruption usually disappears in five or six days, followed by furfuraceous desquamation. In one case the papules increased in numbers until they gave the skin the appearance of "goose-flesh." The eruption was attended by decided itching, and lasted some days after the discontinuance of the medicine. Stewart reports the case of a powerfully built man, who was ordered five-mimim doses of Fowler's solution after each meal. After the sixth dose he felt feverish, and he noticed that his hands and arms were red, swollen, and very hot; the redness of the skin spread rapidly, until it involved the entire surface, except the face. The skin was covered with countless papules, about the size of millet seeds.

Keys, cited by Piffard, reports after the use of arsenic, doses not stated, a papulo-erythematous eruption, dry and livid, on wrists and neck; general papular eruption on trunk and extremities attended with pruritus. Baglie observed dryness of the skin, heat, and itchiness of the eyelids with the production of a minute papular rash, followed by desquamation. Faithful observed a papulous eruption about the face, attended with a decided amount of pruritus. The papules varied in size from a pin point to that of a No. 4 shot; they were discrete and more or less scaly upon their summits. The eruption disappeared after a few days

upon the discontinuance of the drug, followed by furfuraceous desquamation of the parts affected.

The Urticarial Form.—Fowler, whose name is so well known in connection with this drug, in his medical reports on the effects of arsenic, was the first to instance urticaria as one of the results of its employment. According to Imbert Gourbeyre, it is one of the most frequent forms of arsenical eruption. The wheals are white or rosy-red, and extremely pruriginous, differing in no essential particular from urticaria as commonly observed. Berenguier reports the case of a young lady treated with arseniate of iron, which brought out a copious eruption of white, somewhat reddish elevations of the uniform size of a lentil, and accompanied by intense itching. Broadnax states that arsenic produced a rubeolous eruption in two per cent of one hundred and ninety-seven cases in which it was administered.

The Vesicular Form.—The occurrence of a vesicular eruption from the ingestion of arsenic has been recorded by numerous observers. This eruption may sometimes assume an eczematous character which, according to Balfour, may prove extremely obstinate. Ringer says eczema or urticaria may arise, or perhaps vesication or mere desquamation with tenderness of the hands and feet; again he says in arsenical poisoning a petechial papulo-vesicular or wheal-like rash often appears from the second to fifth day.

Finlayson saw an eruption of clusters of vesicles on an inflamed base, extending from lower part of the arm down the back of the forearm and hand, including backs of the fingers. Herpes labialis and preputialis, and an eruption of herpes upon the scrotum, have also been observed from the use of arsenic. Faithful states that in one case herpes

preputialis always made its appearance after giving arsenic for a few days.

It has been asserted that herpes zoster may occur as the result of the ingestion of arsenic in medicinal doses. Hutchinson, while not claiming that a causal connection has been absolutely demonstrated, yet suggests its extreme probability in view of the well-known fact that herpes zoster has been more often observed in patients who have been taking arsenic than in those not subjected to this medication. He reports a number of cases, fifteen or sixteen, in which the coincidence was so marked as to furnish strong presumptive evidence of an etiological relationship. His observations have been supplemented by the experience of many other dermatologists who have noted this coincidence.

The Pustular and Ulcerative Forms.—According to Imbert Gourbeyre, the internal use of arsenic may produce a pustular eruption resembling variola, the lesions terminating in crusts or ulcerations leaving cicatrices.

Orfila has noted, as one of the toxic effects of the drug on the cutaneous system, an eruption of pustules on the face, shoulders, arms, and chest.

Bazin reports a case in which there appeared after minute doses of arseniate of sodium, continued for fourteen days—one-half of a grain altogether—an eruption of discrete pustules in various stages of development, limited to the hypogastrium and right flank. One of the pustular lesions had become transformed into an ulcer, a centimetre in diameter, surrounded by indurated and inflamed tissue. Near by were two large ecthymatous pustules just breaking down in the centres into ulcers; other lesions were passing from a papular into a pustular form. The evolution of the lesion through its various stages, from appearance of papule to cicatrization of ulcer, occupied only a

few days. The patient rapidly recovered as soon as the arsenic was stopped. In this case, as in others, pustular lesions are the points of departure of the ulcerations encountered in various parts of the body, more especially on the head, limbs, and scrotum. Gangrene sometimes occurs around the genitalia.

Erysipelas with bullæ, erysipelatous inflammations about the face and eyelids, and eruptions of a petechial character, affecting by preference the trunk and genital parts, have been recorded by Bazin, Imbert Gourbeyre. and others.

According to Morris, boils and carbuncles occasionally result during a course of arsenical treatment. This statement is confirmed by Foster, Vaudry and others cited by Piffard.

Brownish Pigmentations.—Among the incidental effects of arsenic upon the skin may be mentioned certain grayish or brownish discolorations, which are especially liable to occur upon the face and various parts of the body, after its prolonged use. Wilson reports the case of a patient with gutta rosacea, who had taken arsenic for two months, when there was noticed a change in the color of the skin, first over the abdomen, then on the neck, breast, face, and hands. The face was of a yellowish-brown color, the eyeball dark, the skin of the entire body more or less pigmented ; chronic erythema affected the palms ; there were hard dry points at the orifices of the sweat glands ; the eyelids and the extremities were œdematous. In a case of arsenical dermatitis recently presented by me before the New York Dermatological Society, there was an erythemato-papular eruption, with a grayish-brown, almost black discoloration of the surface, especially marked over the abdomen and inner surface of the thighs. Guaita reports that, in fourteen children placed upon Fowler's

solution for four or five months, there was observed a bronzed appearance similar to that of Addison's disease, beginning on the neck, extending to the chest, then to the abdomen and hands; at times it is seen on the back and legs. It disappears by desquamation in about four weeks. Bazin has characterized this pigmentation as a tint, comparable to the staining of nitrate of silver. This condition depends, according to Gubler, not upon a chemical combination, as is the case in argyria, but on abnormal pigmentation. Wyss saw alopecia areata developed by the prolonged internal use of arsenic. This result he thought due to the effect of the drug upon the trophic nerves of the hair follicles, causing disturbance of nutrition.

As regards the pathogenesis of arsenical eruptions, opinions differ. It is known that arsenic is eliminated, not only by the kidneys, but by the glands of the skin, the mucous membranes, the salivary and lachrymal glands, etc. Chatin found arsenic in the contents of a bulla, and Bergeron and Lemattre in the sweat of patients undergoing arsenical treatment; while Barella claims to have demonstrated the direct elimination of arsenic by the sweat glands. Therapeutically, arsenic has been classed as a neuro-tonic, and is supposed to modify cell nutrition through its influence upon the peripheral nervous plexuses. In view of these facts, we can understand how it may cause disorders of the capillary circulation and disturbances of the nutrition of the skin, as manifested in the various forms of eruptive disorder above described.

The tests for the detection of arsenic are so elaborately considered in text-books that it is unnecessary to describe them in detail. The reader is referred, for information upon this point, to page 58.

The treatment of arsenical eruptions may be restricted

to the simple expedient of suppressing the offending cause. In the more severe forms, the same local measures are to be resorted to as are indicated in dermatitis from other causes.

BALSAMUM PERUVIANUM.

An erythematous and also an eczematous eruption are by no means infrequent from the irritant action of this agent.

Mögling, quoted by Lewin, reports an urticarial eruption following a single application of the balsam of Peru for the cure of scabies in his own person. Redness of the skin in patches appeared on the inner surfaces of the knees and on the shoulders, attended with intense itching. The wheals first appeared on the abdomen, arms, and shoulders. The urticaria successively affected the face, neck, back of forearms, legs, and dorsum of the feet. It disappeared when he removed the woollen shirt he had worn and which was saturated with the balsam, and had taken a warm bath.

BELLADONNA—ATROPIA.

The exanthem produced by the external or internal use of belladonna, or its alkaloid, is usually erythematous in character. It consists of a bright diffuse redness, strikingly suggestive of the rash of scarlatina. It is usually confined to the face and neck, but may extend to the upper portion of the chest, and, exceptionally, may become generalized over the surface. It is quite fugitive, disappearing in the course of a few hours, leaving no trace, and is not, as a rule, followed by desquamation.

The belladonna rash is most commonly and characteristically seen in children with fine, delicate skins, in whom

it appears after small doses of the drug. Its evanescent character is a marked feature.

Lusanna reports a case in which, after a small dose of atropia, the skin became intensely red and presented the appearance of having been exposed to the intense heat of the sun. The erythema lasted from one-half to one hour, and came out each time after taking the drug. Stadler saw a similar eruption appear upon a child within a few minutes after the administration of one two-hundredth grain of sulphate of atropia, which lasted five hours. Smaller doses brought out the eruption each time, but it was of shorter duration. In a case reported by Gray, the face, the upper extremities, and trunk exhibited a diffuse scarlet efflorescence studded with innumerable papillæ resembling very closely the rash of scarlatina. A patient of Dreyfous took two grains of extract of belladonna in three days, followed by a vapor bath. On the night following the third day, there suddenly appeared a scarlatiniform eruption mingled with lesions like those of papular erythema and in places with vesicles. The eruption, which was attended with intense pruritus, occupied almost the entire surface of the body, disappearing on the fourth day without desquamation. Boecke reports a case in which one-quarter grain of extract of belladonna, ordered three times a day to a consumptive patient, produced, after the second dose, erythema and partial gangrene of the skin of the scrotum.

In a case which came under my observation, a child four years of age was given an aperient pill containing one-quarter grain of extract of belladonna which had been ordered for his father. In the course of an hour or two there was an excessive flushing of the face, which soon extended over the body. When I saw him, two hours later, the whole surface of the body presented a " boiled lobster "

appearance; there was redness of the eyes and throat, and mydriasis. The next day the erythema had disappeared, leaving no trace.

Kobner observed a characteristic hyperæmia of the face from the use of suppositories containing extract of belladonna introduced per vaginam.

Wilson reports the cases of two lying-in women who applied belladonna to the breasts to produce galactostasia. On the fourth day a scarlatina-like exanthem came out which disappeared in the course of three or four days without desquamation.

Mackintosh reports a case of herpes following the external use of belladonna and atropine. The application of belladonna liniment to an inflamed knee-joint was followed by an eruption of herpes with a good deal of swelling over the seat of application. Two months later he was ordered a solution of atropine for iritis; some of the solution ran over the cheek, and was in a few hours followed by an herpetic eruption of exactly the same character as had followed the use of the belladonna liniment.

It is a clinical fact familiar to ophthalmologists, that the use of atropine drops, instilled into the eyes, occasionally causes an erysipelatous inflammation about the lids and face, sometimes giving rise to considerable disfigurement. Chislom has recorded a case of severe facial erysipelas from the topical use of atropia.

Liebreich has noted that conjunctivitis, erythema, eczema, and peculiar pearly granulations on the conjunctiva are observed after the long-continued use of a solution of atropia instilled into the eyes.

Fialkowski reports a case in which a solution of atropine instilled into the eyes produced on the second day an erythema and eczema of the eyelids. The atropine being continued for ten days, almost the entire face of the pa-

tient presented a general confluent eczema. The solution being discontinued, the eczema disappeared in the course of ten days. A new instillation of a single drop of a weak solution caused the appearance of vesicles, with pruritus of the borders of the lids.

The belladonna rash derives its chief clinical importance from the fact that it sometimes simulates scarlatina with alarming accuracy, especially when associated with congestive symptoms of the throat and fauces. The bright scarlet hue of the eruption renders this similitude quite complete, although the punctate character of the scarlatina rash is usually not present. The absence of fever and other prodromal symptoms, the dilatation of the pupils, and the transitory existence of the belladonna exanthem soon clear up the diagnosis.

The mode of production of the belladonna eruption has been attributed either to a direct excitation of the sympathetic or to a paralyzing influence of the drug upon the vaso-motor centres, causing dilatation of the cutaneous capillaries. The exceedingly evanescent character of the eruption renders special treatment unnecessary.

BENZOLE.

Lewin has observed that the application of benzole as a parasiticide on the inner surfaces of the thighs and scrotum, and on other sensitive surfaces, causes intense pain, lasting several minutes, which is followed by more or less extensive erythema.

BROMINE—BROMIDES OF POTASSIUM, AMMONIUM, SODIUM, LITHIUM, ETC.

The cutaneous disturbances which may follow the ingestion of the bromine compounds have been long recognized by the profession. All of the salts above enumerated produce similar effects upon the skin. The eruptions recorded as due to the use of bromide of potassium may be regarded as typical of those produced by the other bromine preparations.

The so-called "bromic acne" occurs in so large a proportion of persons who take the bromides that it is difficult to separate these irritative effects upon the skin from the recognized physiological effects of the drug. This proportion is given by Clark and Amory as sixty-six per cent, and by Voisin as seventy-five per cent of all patients treated with bromide of potassium. The latter observer records the fact that, of twenty-four epileptics successively treated, all were affected by bromic acne on the face, scalp, back, and other parts of the body.

The term "bromic acne," it may be remarked, is quite comprehensive in its signification, and has been used to designate a variety of anatomical forms, some of which are in no way connected with disorders of the sebaceous glands.

The bromic eruptions have been most carefully studied by Voisin and Veiel. The classification of the former, which embraced all changes in the skin which had at that time been recognized as due to the administration of the bromides, has been enlarged by the addition of other varieties of eruptive disorder which have since come under observation.

The Erythematous Form.—Veiel describes a diffuse ery-

thema, always limited to the lower extremities, accompanied by high fever, and quite painful. According to other observers, it may occur as a bright-red or dusky-red rash, in patches the size of a finger-nail or a pea, and not absolutely confined to the lower extremities. Bedford-Brown has noticed the occurrence of a roseola from bromide of potassium in children. Comparatively few observations of this nature have been recorded, probably because this drug is seldom administered to children, and not because they are insusceptible to its pathogenetic effects. Carlos reports a case in the service of M. Voisin in which bromide of ammonium produced an eruption of slightly elevated patches of a vivid red color, with subcutaneous induration. The eruption first appeared on the thighs and abdomen, and became general. It disappeared with considerable desquamation.

The Urticarial Form.—Voisinob served in two cases, out of ninety-six upon which his studies were based, an eruption, preceded by pain and pruritus, of oblong or irregularly rounded elevations of the skin of varying size, from one-fifth to two and one-half inches in diameter, and of a rose-red or cherry color. They presented the shape, color, and hard base of erythema nodosum, but resembled urticaria in reappearing when rubbed. These lesions persisted so long as the bromide was given, but they rapidly disappeared on the discontinuance of the drug, always leaving behind the subcutaneous nodosities which were slower in evolution. Veiel also observed coin-shaped, wheal-like elevations, varying in size from one-quarter to one-half inch in diameter, develop on erythematous patches of skin, but only upon the legs. They were very sensitive to the touch, and, if the drug was continued, they took on a suppurative action. Richard, cited by Deschamps, reports the occurrence of an eruption developed upon

erythematous patches, and presenting the objective character of an urticaria, in a boy six years old, from large doses of bromide of potassium. The eruption was distributed over almost the entire surface of the body.

The Papular Form.—The papular bromide rash is most often observed as the first stage of bromic acne, to be succeeded by a papulo-tubercular and pustular stage. Duhring describes a case of maculo-papular eruption, in which small doses of the bromide produced an erythematous condition of the skin of the face and neck, accompanied by a copious eruption of maculo-papules and flat papules. The dark coppery color of the eruption simulated very closely a maculo-papular syphiloderm. Echeverria describes a papular eruption distributed over the elbows and surfaces of the hands, knees, and legs.

The Papulo-pustular Form, "Bromic Acne.—This is by far the most common and characteristic form of bromine eruption. Bromic acne exhibits in the manner of its development, its seat of election, and the anatomical form of its constituent elements many points of similarity, if not of identity, with acne vulgaris. As in acne vulgaris, we find associated papules, tubercles, and pustules affecting by preference regions rich in sebaceous glands, such as the face, back of shoulders, front of chest, etc., but unlike ordinary acne, they often surpass these habitual limits, and they always develop without the antecedent existence of comedones. Bromic acne manifests a special preference for parts where hairs abound; it attacks the hairy scalp, eyebrows, hairy portions of thighs and legs, and many of the pustules are found pierced with a hair. It is not limited to the young, as acne vulgaris. Sex, age, disorders of the reproductive organs, etc., do not act as predisposing causes.

The papular form usually precedes the pustular form.

It is most commonly seen on the hairy scalp, about the forehead and nose and back of shoulders, rarely on other parts, in persons who have thick, greasy skins or a free secretion of sebaceous matter. They commence as pin-head or pea-sized hyperæmic patches developed from an indurated base and surrounded by an areola; the majority of the papulo-tubercles are pierced by a hair. They may remain in this condition for weeks, indolent and without tendency to undergo progressive change, or they may rapidly develop into the pustular form.

The pustules are of a yellowish-white color, similar to those of acne vulgaris, and may sometimes present an ecthymatous aspect. Sooner or later the contents of the pustules are discharged, and a firm indurated nodule or a pigmented spot remains. After healing, they not infrequently leave small depressed, rounded cicatrices. The pustular condition may persist almost indefinitely if the use of the drug be continued. Veiel found that the number and development of the pustules increased with the augmentation of the dose. Exceptionally, it has been observed that the eruptive accidents, after having persisted for some months, rapidly disappear and are not again reproduced, although the medicine may be continued in the same or augmented doses. Ordinarily, the eruption disappears in the course of one to three weeks after suspension of the drug.

Voisin describes an eruption of small tumors formed by groups of indolent acneiform pustules, inflamed at the base and depressed at the centre, very painful to the touch, except at the centre, which is anæsthetic. They discharge a matter like that of furuncles, and are sometimes transformed into foul atonic ulcers, which heal slowly and leave cicatrices. They are usually seated upon the legs, and may coexist with acne over other parts of the body.

Confluent Acne.—Under the designation of "confluent acne," Cholmely has described an eruption occurring in a boy thirteen years old who had taken twenty-five grains of the bromide three times a day for a week. The eruption was at first varicelliform, but the vesicles, instead of drying up, became in many places confluent, the clusters so formed continuing to enlarge and showing numerous points of suppuration. The eruption, though occurring on other parts of the body, was most active on the legs. The lesions were of various sizes, from a pea to a four-penny piece, larger than those on the face, irregularly oblong. The most recently formed consisted of a prominent circular vesicle, filled with milky white semi-fluid matter, seated on a slightly elevated and hardened base, and surrounded by a vividly red areola, pierced by one or more broken hairs. The larger spots were flattened elevations, covered by a flaccid cuticle or thick light-brown crusts, and surrounded by a dark-red areola. On removal of the crust, the surface beneath presented numerous millet-seed-like, yellowish protuberances. The eruption died away after seven weeks' duration. The bromide, in full doses, redeveloped the eruption on the sixth day.

Neumann states that he has observed an eruption very much like molluscoid acne coming out in successive outbreaks, and in another case a carbuncular eruption, consisting of infiltrated tumors, with considerable loss of substance in the centre.

The Furuncular and Anthracoid Forms.—A furunculoid eruption has been observed by Voisin and many others.

Smith and Neumann saw numerous boils on different parts of the body from the use of the bromides; the latter observed them on the hairy portions of the face and on the forehead and neck. These boils were for the most part of small size, and without central core. It is doubtful

whether they differed in their anatomical seat from ordinary boils.

Quite recently I have observed an eruption from the prolonged use of bromide of potassium which cannot be grouped with any of the preceding forms.

In June, 1886, a patient who had been taking a mixture of bromide of potassium and tincture of iron almost continuously for several months presented himself, with a large carbuncular swelling upon right arm at the insertion of deltoid. He stated that three days before it appeared as a "large reddish pimple," which within twenty-four hours developed into a blister. This broke the following day, showing four or five openings from which pus exuded.

Within the next two weeks similar lesions developed upon other portions of the body. One appeared upon the left wrist, two on inner side of left thigh, two on right leg, one on left cheek, and another on the back of the right shoulder near posterior axillary space. I had an opportunity of watching the mode of their formation and evolution, which was as follows: First there appeared a circumscribed inflammatory swelling which in twenty-four hours was surmounted by a flat bulla, filled with a sero-purulent fluid. The swelling rapidly increased in depth and extent, resulting in the production of a hard phlegmon, surrounded by an intense inflammatory areola two or three inches in diameter. Upon rupturing the blister, there was disclosed a number of openings, from which a rather thin pus could be pressed out. On probing, the openings were found to be shallow. The lesions differed from ordinary anthrax in their more indolent and superficial character, the comparative absence of pain, and the rapidity of their involution. After the bromide was discontinued, they disap-

peared within a few days under the influence of dressings of camphorated oil.

The Ulcerative Form.—Seguin has narrated three cases in which a peculiar cutaneous lesion, termed by him *ulcus elevatum*, was produced by bromide of potassium. The lesions were described as large, irregular, ulcerated patches raised from two to four millimetres above the surface, symmetrically situated on legs. The elevated floor of the ulcer was firm, grayish-red in color, with here and there an adherent crust. It secreted a sanious, fetid, puriform liquid, and bled upon being touched. It did not look like ordinary granulating tissue ; it was much firmer and composed of large masses. At several points it presented a slightly villous or rather papillomatous appearance. The cicatrix of a similar lesion, which had existed ten years ago, was seen. The patient at that time had been taking large doses of the bromide. In the third case, the lesion had been twice developed by bromides, but it was more carbuncular in character.

Amidon describes what he terms an "epithelial ulcer," peculiar to the prolonged use of the bromides in large doses, of which he had observed two or three cases. It begins as a large-sized, single acne spot, with a large base, which apparently takes on an inflammatory process and afterwards breaks down into what appears to be a simple ulceration. Vesicles appear in circular form about the ulcer, the contents of which become cloudy and purulent, and are finally covered with dark-colored crusts. The centre of the affected surface heals, while a superficial ulcerative process extends at the periphery sometimes to the distance of several centimetres. The true skin is not involved ; the process simply denudes the skin of its cuticle, with hypertrophic changes affecting the papillæ.

Sangster reports a bromide eruption presenting the fol-

lowing characteristics: On the outside of the right leg there was a round, considerably raised patch, about the size of half a crown. The surface was partly crusted; here and there it exhibited little subcutaneous dots of pus closely set together. There was a crop of smaller blotches over the same thigh and buttock, the size of a three-penny piece, elevated and partly covered with a brownish crust. Two symmetrical groups of similar lesions, four in number, on either side of the face, completed the eruption.

The Verrucose Form.—Veiel records an anomalous form of bromine eruption in which he observed large, wart-like prominences upon the face, cheeks, nose, and eyebrows of a boy 16 years of age, soon after he commenced taking the bromides. These lesions exactly resembled the verruca ordinarily seen upon the hands of young persons. This phenomenon has not been encountered, or at least recorded, by other observers, and it may have been a coincidence, rather than an effect directly due to the drug.

The Vesicular Form.—In Voisin's classification of the various forms of bromine eruption, he reports a case coming under his observation of moist eczema of the legs, with pityriasis of the scalp, in a patient who had never before suffered from any cutaneous affection. So far as I have been able to ascertain, there has been no similar observation recorded in the literature of this subject.

The Bullous Form.—Wigglesworth reports a case of a lady in whom bromide of potassium produced an eruption of bullæ which were somewhat acuminated, and varied in size from that of a pea to that of the end of the finger. Some of the bullæ appeared to contain blood, and, on rupturing, exposed an ulcerated surface.

In addition to the various forms of eruptive disorder from the use of bromide of potassium already noted, Veiel and others have described a squamous eruption, sebor-

rhœic in character, preceding or co-incident with the outbreak of acneiform lesions.

Clinical experience would appear to indicate that there is no essential difference in the pathogenetic influence of the various salts of bromine. Numerous observations have shown that the bromides of sodium and ammonium exercise the same irritating effects upon the skin as the bromide of potassium.

Pathological Anatomy.—The pathological histology of the various lesions has not been carefully studied. Neumann made a microscopical examination of a pustular lesion in a child resulting from the ingestion of twelve scruples of bromide of potassium. He found the sebaceous glands, the hair-follicles, and the upper part of the corium to be the seat of the disease. The papillæ were increased in size, and the whole of the corium highly developed. The most marked feature of the changes was epithelial hyperplasia.

Seguin gives the histology of the lesion reported by him as follows: Sections of the piece of tissue removed from ulcer showed great increase in the thickness of the rete Malpighii, with hypertrophy of the whole skin in places. The deeper layer of the skin and, to a certain extent, the subjacent connective tissue are infiltrated at certain points with young cells. The papillæ, hair-follicles, and sweat glands do not appear to be the seat of any primary or important inflammatory change.

Pathogeny.—Various theories have been advanced to explain the mechanism of the production of the bromine eruptions. From the fact that certain forms of bromine eruption, especially the papulo-pustular, appear in such a large proportion of all cases treated with the bromides, it is evident that idiosyncrasy, which plays so important a rôle in the production of other drug eruptions, does not

figure prominently as a predisposing element. Without being constant, they are sufficiently common as to lead to the belief that they are, in a great measure, independent of individual predisposition, and may be developed in almost every case, provided the dose be sufficiently large and long continued. The changes which take place in the skin, like other symptoms of bromine cachexia, may, therefore, with propriety be classed among the exaggerated physiological effects of the drug, and it is plainly within the sphere of the nervous system that we must seek an explanation of these effects.

It is well known that the alkaline bromides are eliminated principally by the kidneys, as well as by the salivary, lachrymal, and sudoriparous glands in a less degree. It has been claimed that the sebaceous glands may also participate in this excretory action, and that the cause of the cutaneous disturbance observed after the internal administration of the bromine salts is the irritation attending the elimination of the drug through this channel. Plausibility is given to this hypothesis by the experiments of Guttman, who found bromine in the contents of the pustules. On the other hand, Veiel and numerous other observers have failed to find the drug in any of the cutaneous lesions caused by its use, although it is always readily detected in the urine. While they do not deny the possibility of its excretion through the sebaceous follicles, yet they contend that the quantity thus eliminated is too minute to set up inflammation of the follicle, and thus give rise to acne by direct irritation. Clark and Amory regard bromine acne as a tropho-neurosis resulting from the direct action of the bromide upon the peripheral nerves, producing a derangement of the nutrition of the skin, of which the eruption is the outgrowth.

Diagnosis.—The appearance of the bromine rash is sel-

dom attended with fever and other symptoms of constitutional reaction. As compared with other drug eruptions, it is more gradual both in its development and decline. The acneiform eruption is most often observed after the use of the drug in small doses has been continued for a long while. It increases in severity with the augmentation of the dose, and declines with its diminution. These characteristics have a certain importance from a diagnostic point of view, although there are few affections of the skin with which it could be confounded. In the maculo-papular form, its brownish-red or copper tint might suggest syphilis. It is more liable, however, to be confounded with acne vulgaris, from which it may be differentiated by the absence of comedones, its development at periods of life which would exclude ordinary acne, and on parts of the body where this latter affection does not occur. Its association with other symptoms of "bromism," especially fetor of the breath, and the presence of bromine in the urine, would leave no doubt as to the diagnosis.

Tests for Bromine and Bromides.

Both bromine and iodine are liable to escape detection if an attempt is made to set them free in the urine. This is particularly the case with bromine. The reason is that both are prone to combine with some of the organic constituents of the urine, forming substitution compounds. To avoid error, it is best to proceed as follows:

Render the urine alkaline with potassa, evaporate it to a small bulk, transfer this to a crucible, and apply heat gently, until the contents are apparently dry and somewhat charred. Then cover the crucible, and heat it to a *low* red heat until the mass is carbonized. Allow to cool;

add water and boil for a short time, then filter. The filtrate, with washings, will now contain, besides other inorganic salts, any iodine or bromine in form of iodide or bromide.

Concentrate the filtrate, and add to a portion of it some disulphide of carbon, and afterwards *dilute* chlorine water, drop by drop, shaking after each addition. If bromine was present, the disulphide will assume a yellow or yellowish-brown color. Should it have a violet tint or color, iodine is present. In this case, the test is to be applied very slowly, and chlorine water added as long as the color of the disulphide deepens, when this is to be removed and the test continued with a fresh portion of disulphide as above directed.

Treatment.—The main indication in the treatment of the cutaneous disorders caused by the internal use of the bromides is the suppression of the exciting cause. In certain conditions, however, the nervous symptoms of the patient may be of a nature to render the continuance of the medicine desirable, if not imperative. In order to realize the full therapeutic advantage of the drug, without its inconveniences, a number of adjuvants or correctives have been recommended. Arsenic has been recommended by Bartholow, Gowers, and others. Gowers found that five-drop doses of Fowler's solution caused the pustules of bromic acne to disappear in two weeks. This was evidently a post hoc conclusion, since experience teaches that the cutaneous eruption usually vanishes in this time without any treatment whatever. Sulphide of calcium is another drug which, on account of its well-known anti-pyogenetic influence, has been recommended to antagonize the tendency to the formation of pustules. Seguin found, however, that both arsenic and sulphide of calcium failed to influence the eruption in his cases.

Another expedient which suggests itself would be to give the bromide in doses just short of those sufficient to cause irritative effects upon the skin. But Falvet claims that the favorable results from bromide of potassium only begin to appear when an eruption of pimples appears on the skin of the face. Brown-Sequard thinks that the cropping out of an "acne-like eruption on the face, neck, and shoulders," etc., is an evidence that the bromide is proving curative, and he asserts that there is "a positive relation between the intensity of the eruption and the efficacy of the remedy against epilepsy."

CALX SULPHURATA. SULPHIDE OF CALCIUM.

The eruptive disturbances which follow the internal use of sulphide of calcium are chiefly of a pustular or furuncular character. It is only recently that the use of the drug has been revived, on the recommendation of Ringer, and the literature of its incidental effects is necessarily limited.

Hahnemann, quoted by Piffard, states that the calx sulphurata taken internally may cause vesicles, pustules, and furuncles on the healthy skin.

Alexander gives notes of three cases coming under his personal observation in which the ingestion of sulphide of calcium in varying doses produced a crop of furuncles distributed over the face, neck, forearms, wrists, and other portions of the body, accompanied in each instance with constitutional disturbance more or less severe. The dose in one case was eight grains three times a day, in the second one-tenth grain, and in the third one-quarter grain three times a day. The direct dependence of the eruption upon the use of the drug was inferred from the fact

that amendment of the symptoms began in each case immediately upon suspension of the drug.

The following case came under my observation. A large, robust, florid-faced man, who had suffered for some months with successive crops of boils upon the back of the neck, was ordered pills containing each one-quarter grain of the drug, one pill to be taken three times a day. The furuncular eruption began to disappear soon after commencing the use of the pills, but some days afterwards he called my attention to certain spots which had appeared on the lower limbs. On examination, they were found to consist of a scattered eruption of pin-head to pea-sized petechiæ, extending from the dorsum of the foot upwards above the knee. They were most abundant upon the calf, a few were seen upon the anterior surface of the thigh, none upon the trunk or upper extremities. I counted about one hundred altogether. Upon discontinuing the pills, the spots slowly disappeared in the course of ten days or two weeks.

As I was not positively certain of the relation between the drug and the eruption, I again ordered the pills in the same dose. All doubt as to the causal connection was soon set aside by the reappearance of the petechial spots with almost the same localization as before.

In another case, in which I gave sulphide of calcium in one-half-grain doses for the relief of a furuncular affection of the face and neck, there appeared a number of large pustules upon the wrists, backs of the hands, and fingers. Whether this eruption was due to the influence of the drug, or was a further manifestation of the same pyogenetic tendency exhibited in the furuncular inflammation, could not be determined by further experiments, as the patient passed from my observation.

CANNABIS INDICA.

The well-known physiological action of Cannabis indica upon the sensory nerves of the skin, producing a marked degree of numbness and tingling, would lead to the inference that it possesses the property of causing cutaneous disturbances of an eruptive character.

The only case of eruption from this drug found in the literature of the subject is recorded by Hyde. The patient had taken one grain of the extract. The next morning, the surface of the scalp, face, ears, neck, trunk, and extremities, including palms and soles, was found covered with an eruption of thickly disseminated vesicles, in size from a pin-head to a split pea. The vesicles were developed upon the summits of papules ; they were not grouped and did not coalesce, and occasioned only a moderate pruritus. The eruption subsided within a few days without treatment; the vesicles shrivelled up without bursting. After desiccation, the crusts fell off, leaving a transient pigmentation.

CANTHARIS.

The application of cantharides to the skin, in the form of ointments, cerates, or as cantharidin, causes a sensation of tingling and smarting succeeded by pain, redness, vesication, and the production of bullæ which unite to form a large blebs containing a pale-yellow, serous, watery fluid rich in albumin and fibrin.

According to Trousseau, the skin about the blister, especially in persons of the dartrous diathesis, may become covered with vesicles, at first separate, but afterward confluent, forming a genuine eczema; pustules of impetigo may also appear. The eczema, at first limited to the

region where the blister was applied, often extends by degrees in an acute form to the entire surface of the body. In persons of enfeebled constitution, ulceration, anthrax, furuncles, even gangrene of the affected surface may occur; or it may become the starting-point of erysipelas. Trousseau records the case of a female patient to whose thigh he ordered a flying blister for rheumatism; it was dressed with diachylon plaster. A few days later, there appeared around the sore a vesicular eruption which soon invaded the entire surface of the body, causing high fever. This condition was replaced by a pemphigus which lasted some months. Pereira mentions a case in which the application of a blister to the pectoral region caused the development of ecthymatous pustules, not only over the region of application, but also over the entire body.

In a case reported by myself, the introduction of cantharides by acupuncture for inflammation of the knee-joint caused intense inflammation of the penis and scrotum, with complete exfoliation of the epidermis of these parts; also strangury and hæmaturia.

Erythematous and papular eruptions affecting other parts than the genitals may follow the internal use of cantharides.

Tests for Cantharides.

It is only when large doses of this drug have been taken, or when it has been taken for a certain length of time, that the presence of cantharidin can be demonstrated in the urine. The principal reliance is based upon the vesicating power of the matter extracted, unless the quantity of cantharidin should be large enough to apply chemical tests, which is but seldom the case.

Cantharidin may be extracted by shaking a liquid containing it, after rendering it strongly acid, with chloro-

form. The suspected urine is concentrated to one-fourth, rendered strongly acid by sulphuric acid, and then twice successively shaken with an equal volume of chloroform. The united chloroformic solutions are repeatedly shaken with water, then evaporated to dryness (or as far as possible), the residue heated with a little fixed oil of almonds, and a small piece of lint saturated with this oily solution applied to the breast covered with a little court-plaster. If notable traces of cantharidin were present, there will be more or less vesication.

CAPSICUM.

Capsicum is stimulant and irritant to the skin and mucous surfaces. Its local application causes pain, itching, and redness, and, if sufficiently prolonged, produces vesication. Phillips says that, applied to the skin, especially in a concentrated solution, capsicum is a powerful rubefacient, and will even blister, if applied continuously.

Taken internally in large doses, it produces a general glow of the surface, sometimes an erythematous eruption.

Allen states that teaspoonful doses of a solution of capsicum, taken at night, caused a papulo-vesicular eruption all over the body, with much burning and itching.

CHLORAL.

The effect of the topical application of hydrate of chloral is irritant, and if the skin be deprived of epidermis, it causes a sharp, burning pain. Cantani pointed out that its external application produces erythema and vesicles surrounded by capillary hyperæmia. More recently, Ritter has called attention to the fact that chloral has many points of superiority over cantharides as a vesicant. He found that powdered chloral sprinkled over ordinary adhesive plaster slowly melted, and applied while warm to the skin, causes in three minutes a gentle heat, increasing in intensity for about three minutes until it is like a burn, then easing off, until at the end of ten minutes the parts feel free from pain. If the plaster be now removed, "the surface is found as effectually denuded as by a cantharidal plaster after six hours' application, although the discharge is not so great."

The eruptions which follow the internal administration of chloral are comparatively infrequent, considering the extensive employment of the drug. It is claimed that, since improved methods of manufacture have been introduced, which insure a greater purity of the drug, from the elimination of certain deleterious chlorine compounds formerly present, the frequency and severity of incidental irritative effects have been much lessened. There is no doubt, however, that individual predisposition plays an important rôle in their production. While the type of the chloral rash is erythematous, a variety of eruptive phenomena have been observed from its internal use.

The Erythematous Form.—A diffuse hyperæmia is the most common of the incidental effects of chloral upon the skin. It usually appears as a uniform redness or a bright

flush upon the face, and may then successively affect the neck, chest, and extremities. Its places of predilection, after the face, are the extensor surfaces of the lar gearticu lations, knees, wrists, elbows, and ankles. It is a notable fact that, while it almost always appears as a diffuse redness upon the face, upon other portions of the body it occurs in patches, or as dusky red spots with irregular borders, giving the skin a somewhat mottled appearance. Ordinarily it is transient in duration and is not attended with subjective sensations or constitutional disturbances.

The chloral rash is usually developed within a short time after commencing the use of the drug, rarely delayed longer than the tenth day. All observers have noted the fluxionary character of the hyperæmia; indeed, one of the most characteristic features of the eruption is the remarkable influence of hot drinks or a full meal in its production. Always after the ingestion of food, tea, alcohol, etc., the rash becomes more intense and generalized. After suspension of the chloral even, the rash may continue to reappear for several days after each meal. The tendency to cutaneous irritation seems to remain latent until roused into activity by some stimulant to the vascular system. It then develops suddenly, remains out for a variable interval, one to two or three hours, and then vanishes, leaving no trace of its passage, except in some cases a slight furfuraceous desquamation.

In other cases, the rash may appear as an inflammatory redness, which is strikingly suggestive of the scarlatina exanthem, and may spread over the entire surface of the body. This similitude to scarlatina is rendered more exact by the increased sensitiveness of the skin, the high fever, and the more or less abundant desquamation which follows.

Kobner reports a case in which there appeared, not a

simple hyperæmic redness, but an erythema exudativum which spread over nearly the entire surface. The skin was more swollen and infiltrated than in scarlatina, to which it bore a strong resemblance. It was attended with burning and itching and, as the use of the chloral was persisted in for some time, it ended in desquamation in the course of four or five weeks.

The Papular Form.—Kirn reports a case of an eruption of papules situated upon red bases occurring upon the arms. Arndt reports a case in which doses of from two to five grains produced on the eighth day a papular eruption, consisting at first of scattered lesions which, later, coalesced into wheal-like patches. It appeared successively on the hands, forearms, chest, and face, and gradually spread over the whole body. It was followed by icterus. The eruption and the icterus disappeared on the suspension of the chloral. A papular eruption followed by jaundice was again developed a month later by giving the chloral in same doses.

Litten gives notes of the case of a girl who swallowed twelve and one-half drachms of chloral at once. In addition to other symptoms of chloral poisoning, there appeared within twenty-four hours a general eruption of conical or globular papules of yellow color, more numerously developed between the fingers and upon the face and breast. The eruption was quite itchy, and lasted about a week.

The Urticarial Form.—Gauchet, Chapman, and others have observed a profuse eruption of urticarial wheals covering the entire surface of the body, attended with the usual subjective sensations of burning and itching. These eruptive phenomena appeared and disappeared with the renewal or cessation of the drug. Kirn reports cases of œdematous or urticarial swellings of skin over the whole

body, which he ascribes to serous infiltration of the skin from stasis of blood.

The Vesicular Form.—A vesicular eruption which may develop into a pustular form sometimes occurs from the use of chloral. Kirn reports the case of a young woman in whom there appeared, on the ninth day of chloral treatment, an eruption in the form of groups of red spots which soon became confluent. On the twentieth day of the treatment, œdema of the cheeks, face, and eyelids appeared, and the skin presented at one time the appearance of a moist, at another, of an impetiginous, and at still another, that of a squamous eczema. The process of desquamation continued for many weeks, during which great sheaths of epidermis were cast off from all portions of the body. Profound disturbances of the skin nutrition were manifested by complete shedding of the nails of both hands and feet, and by the sixth week large abscesses had formed about shoulders and armpits. The chloral was continued all this while, as the physician failed to recognize its association with the eruption. There was continuous fever, the temperature at one time reaching 106.7°.

The Petechial Form.—Brown reports a case in which the drug was given in twenty-grain doses three times a day. On the fourth day, a redness, not effaceable by pressure, was observed over the skin of chest and shoulders. Two days afterwards, the eruption had extended over the whole trunk as well as the limbs, deep red patches and livid spots alternating. The patient gradually recovered, desquamation occurring on the fifteenth day. Brown reports another case, in which forty-five grains of chloral, taken daily, produced on the nineteenth day a petechial eruption which rapidly became generalized. Patient died on twenty-sixth day. Kirn refers to a case observed by Monkton, in which the use of sixty grains of chloral daily

produced on the fourth day a rash resembling variola with hemorrhagic purpura. Two similar cases are reported by Pelman.

Reimer had observed, after large doses of chloral, lesions varying from circumscribed redness and swelling of the skin to deep ulcers, with formation of blisters on the trochanters, on the knees, tips of fingers, face, ears, and other parts, and more or less extensive bed-sores when the patient has lain long in one position. Reimer refers these changes to anomalies of the circulation brought about by the paralyzing influence of chloral upon the vaso-motor centres.

Pathogeny.—A number of theories have been offered in explanation of the irritative effects of chloral upon the skin. The striking analogy which the chloral rash presents with the erythema provoked by copaiba, both in its appearance, and in its predilection for the articulations, has suggested the hypothesis that it may be due to the direct action of chloral upon the glands of the skin. No such mode of elimination has been demonstrated in the case of chloral, and such a hypothesis is clearly untenable. Other authors regard it as the result of chronic blood poisoning with determination of the morbid phenomena towards the cutaneous surface. However probable this theory may seem in the exceptional case recorded by Kirn, in which large doses were continued for many weeks, resulting in profound disturbances of nutrition, yet it is manifestly inadequate to explain the more common and characteristic forms which often promptly appear even after small doses.

The theory most in accord with a rational interpretation of the pathological phenomena is based upon a recognition of the influence of chloral upon the vaso-motor nerves. According to this theory, the chloral erythema is

an angio-neurosis caused by a paralysis of the vaso-motor centres of the head and neck. Whether this is due directly to an impression of a particular nature exercised upon the nerves of the stomach and the ganglia with which they are connected, or whether it is caused by an action of the drug absorbed into the circulation upon the nerve centres, is a matter for future inquiry. The urticarial and purpuric forms may also be regarded as an expression of neurotic disturbance.

Diagnosis.—Little difficulty should be experienced in the diagnosis of the chloral eruption. From measles and scarlatina it may be differentiated by the absence of fever, catarrhal symptoms, characteristic throat and tongue, etc. It may be confounded with the erythema produced by belladonna, copaiba, and quinine, respectively. The belladonna rash is almost always accompanied with mydriasis, dryness of the fauces, etc. The chloral rash has special features of its own, such as the absence of subjective sensations, its liability to development after the ingestion of alcohol or a full meal, which serve to distinguish it. The peculiar odor exhaled in copaibic eruptions is always of diagnostic value.

Tests for Chloral.

If chloral is to be detected in urine, the latter is mixed with about one-fourth volume of alcohol, then rendered neutral, if necessary, by either carbonate of magnesium or tartaric acid, as the case may be, and distilled until only a syrupy residue remains. The distillate now contains the chloral. This is recognized by its products of decomposition, viz., chloroform and formate of ammonium (or of other alkali), when the solution is treated with an alkali. The distillate is, therefore, rendered alkaline with soda, and again distilled. The new dis-

tillate will contain the chloroform, which is identified, as shown below. The formate is recognized in the residue by the fact that the latter promptly reduces nitrate of silver to a metallic state—a portion of the residue, when heated in a test-tube with solution of nitrate of silver, producing a brilliant metallic mirror.

The chloroform in the distillate is recognized by converting it into isonitril—a body of a penetrating and disagreeable narcotic odor. This is accomplished by adding to the aqueous solution suspected to contain chloroform some alcoholic solution of potassa, then a drop or two of aniline, and warming. The peculiar odor of isonitril or phenyl-isocyanide will make its appearance. The same reaction is afforded by iodoform, but in the case of chloroform no iodine can be set free as in the former (see Iodoform).

Treatment.—No special treatment is required for the relief of the irritative effects of chloral. No drug given in combinatiou appears to exert a corrective influence. The eruption disappears spontaneously soon after the discontinuance of the drug.

CINCHONA.—QUINIÆ SULPHAS.

The various eruptions which have been grouped under the general term "quinine exanthemata" follow indifferently the exhibition of any of the preparations of cinchona. Since the introduction of the alkaloid to the profession in 1820 it has been almost universally employed to the exclusion of the crude bark, which fact will explain the far greater number of eruptions recorded under this head. While it is presumable that cutaneous disturbances have frequently followed its use from the time of its first introduction, it is worthy of note, that prior to 1870, with the exception of five cases under the care of

Mr. Bouchut in the Hôpital de la Pitié, in which there was observed an erythematous eruption from the ingesting of quinine, no such results have been recorded.

Although the casual contact of quinine with the healthy human skin does not act as a irritant, yet it has been observed that workers in quinine factories are subject to eruptions of various kinds. Evidently these effects are not due solely to external irritation, but in a great measure to absorption of the quinine emanations. Chevallier called attention to the fact that the fabricants of quinine often suffer from affections of the skin, characterized by the development of papules, vesicles, and pustules on different parts of the body, particularly the hands, arms, and legs. Bergeron and Prost have made a careful study of these eruptions and describe them as habitually sudden in their development, involving most frequently the hands, forearms, internal surface of the thighs, and the genital regions. The eruption is usually eczematous in character. Upon patches of reddened skin are observed numerous vesicles, confluent and exulcerated at certain points; in other parts, the serosity has dried up and given place to scales and crusts. Instead of ordinary vesicles, there may be larger lesions resembling the veritable bullæ of pemphigus. Sometimes quite extensive surfaces are seen deprived of epidermis, red and œdematous. The face may be swollen and covered with crusts of eczema, the eyes weeping and injected. This condition readily subsides in the course of a few days under the influence of emollients, protectives, etc.

Monk found, upon passing a current from ten Grove's elements through the body, the electrodes having been moistened with a solution of quiniæ sulphatis, that the surfaces acted upon became, first dry and anæmic, but in the course of a few hours they became hyperæmic and cov-

ered with a number of pin-head sized extravasations of blood, which remained after the hyperæmia had subsided.

Delioux de Savignac reports a case in which the application of a pomade containing sulphate of quinine produced intense pruritus and an eruption of lichen. Quite recently, I observed an urticarial eruption in a young lady patient suffering from phthisis, resulting from the topical application of a solution of one drachm of quiniæ sulphatis in one pin of alcohol, which I had ordered for the relief of night sweats. The wheals were abundant, and distributed over the entire surface of the body, and they continued to recur for two or three days, until I ordered the application discontinued, after which they promptly subsided.

Taylor records a case of a young woman in whom a well-marked dermatitis was developed every time she took quinine internally. She began to use a "rum and quinine" hair tonic, and wherever the quinine preparation came in contact with the skin it caused a dermatitis identical with that caused by the the ingestion of the drug. A similar case came under Otis' observation.

According to Aitken, irritability of the skin, extensive erythema, ulceration, and abscesses at the point of injection, with painful and inflammatory nodules of the subcutaneous cellular tissue, are not infrequent results of the hypodermatic injections of the salts of quinine.

The eruptions which follow the ingestion of quinine are multiform in character. The prevailing type of the quinine exanthem is erythematous, but every form of ele mentary lesion—macules, papules, wheals, vesicles, bullæ, pustules, purpura, etc.—have been observed as the direct result of the administration of this drug.

In a study of the eruptions produced by quinine, published in the *New York Medical Journal*, March, 1880, I

gave the result of my examination of sixty cases of quinine eruptions, published within the previous ten years. Analysis of these cases shows that the different forms of the eruption were represented as follows:

The Erythematous Form.—In thirty-eight of the sixty cases referred to, the general character of the eruption was erythematous. It was further described as "scarlatinal," "scarlatinoid," "bright red," "measly," "rubeolous," "papular," "erysipelatous." In most cases, it appears as an efflorescence of a bright, vivid hue, disappearing on pressure, and closely resembling the rash of scarlatina. Usually it first shows itself upon the face and neck, but soon becomes diffused over the whole surface of the body; in exceptional cases, it may not become generalized, or it may appear in the form of distinct red spots, which become confluent and patchy, and the coloration may exhibit a darker hue, resembling that of measles. The eruption promptly disappears upon the discontinuance of the drug, and is usually followed by desquamation of a branny or lamellar character. In one case, desquamation continued for three months.

The Urticarial Form.—The eruption may present itself with the typical wheals of urticaria. In twelve of the cases, the eruption was described as "urticarial" with "œdema," "puffiness of the face," etc. In this class of cases there is more or less œdema of the face, and the subjective sensations of burning, tingling, and itching are quite distressing. The general features of the following case are typical of this form. In November, 1875, I had occasion to prescribe sulphate of quinia, in two-grain doses, to a gentleman suffering from some bronchial trouble. He took the first dose late at night on going to bed. Soon after he began to experience a feeling of oppression in his chest and a sensation as if his throat were

filling up, accompanied with the most intolerable burning and itching over the whole surface of the body. When I saw him, the face was œdematous, and the entire surface was hyperæmic, and covered with wheals, most abundant about the face and neck. These symptoms subsided during the day, and I advised him to take another dose of the quinine the succeeding evening. Its repetition was followed by a redevelopment of the urticarial rash, and I now suspected that the two might stand in the relation of cause and effect. I gave no more quinine, and his cutaneous troubles speedily vanished. The patient, who was a retired physician, was as much surprised at these unusual effects of the medicine as myself. He had formerly practised medicine in a malarial district, and had been accustomed to take large doses of quinine without experiencing anything beyond its ordinary physiological effects. Two years later, he suffered from malarial trouble. Remembering his former unfortunate experience, he did not at first take quinine, but, curious to test his vulnerability, he finally decided to try it in one-grain doses. In less than an hour after taking the first dose, he had a violent attack of urticaria which affected the mucous membrane of the throat and fauces, as well as the entire surface of the body.

The Papular and Vesicular Forms.—In a few cases, the eruption was described as papular or vesicular in character. In a case reported by Denk, the eruption presented the features of an eczema. The papules, developed upon an erythematous or scarlatiniform base, were transformed into vesicles. The vesicles, pin-head in size, were more abundantly distributed about the neck, chest, and axillary region. After the drug was discontinued, the vesicles dried up, and desquamation occurred in scales or large lamellæ. Reveillod ordered a patient seventy-five

centigrams of quinine three times a day. The third day, he complained of intense burning and itching on palms, forearms, thighs, and feet, which was followed by an erythemato-papular eruption. The patient had formerly worked in a quinine factory, but had been compelled to quit his employment on account of the irritating effect of the quinine. In Heusinger's case, an eruption resembling erythema exudativum multiforme, attended with œdema of the lids, appeared on the face of a lady after taking one-half grain of quinine. On another occasion, one and one-half grains of quinine produced an eruption of herpetic vesicles on the cheeks of the same patient.

Otis relates a case in which a vesicular eruption, some of the vesicles being larger than a pea, had been produced and re-produced by the internal use of quinine. In one instance, two or three grains produced a severe eruption resembling that from poison ivy. The same eruption followed the employment of a hair wash, of which quinine was an ingredient.

The Petechial Form.—A number of cases of purpuric eruption from quinine have been recorded. Moneret (cited by Deschamps) observed small ecchymoses spread over the surface of the abdomen of a patient who had taken quinine. Briquet saw in a patient taking three grams of quinine a day a large ecchymosis develop upon the buttocks and external surface of the thigh, and at the same time a petechial eruption coincident with a sanguinolent diarrhœa. I have observed a purpuric eruption in the case of a boy twelve years of age suffering from malaria, who was ordered by his physician the following treatment: Five three-grain pills of quinine the first day, four the second, three the third, two the fourth, and one the fifth day. Before he had completed this course, an eruption of purpuric spots appeared on the body, more

abundantly distributed on the lower extremities. They disappeared in the course of ten or twelve days after discontinuance of the medicine. Wigglesworth observed an eruption of non-elevated, irregularly circular patches situated upon the forearms and ankles. They were attended with burning and itching, and were painful on pressure. The spots appeared one hour after taking a one-grain pill of quinine, and, under the continued use of the pills, until twelve were taken, the lesions increased in size and number, and became well-marked hemorrhagic patches. Vepan, cited by Jeudi di Grissac, reports four cases in which an eruption of petechial spots occurred over the whole body from the use of comparatively small doses of quinine. In the case of a lady who took first 0.1 and later 0.15 gram, the eruption increased in violence and extent with the increase of the dose. In this case, the purpura was accompanied with bleeding from the gums and sanguinolent stools.

Gauchet reports a case in which the intolerance of quinine was so absolute that small doses, only ten centigr., continued for four days, produced purpura with buccal hemorrhage, principally from the gums. The petechial spots were abundant and generally distributed. In this case Gauchet gave quinine in opposition to the wishes of the patient, who stated that she had taken it before and that it always caused her to spit blood.

The Bullous Form.—This form is comparatively rare, but the possibility of its occurrence is well authenticated. M. Panas, cited by Bergeron and Prost, affirms that the administration of large doses of quinine (two to three grams, as is the custom in Algiers and Greece) provoked an eruption resembling the bullæ of pemphigus.

Fowler reports a case in which four grains of bisulphate of quinine produced an eruption of bright-red patches,

varying in diameter from one-half to two inches, over wrists, forearms, knees, and ankles; twenty-four hours later, the spots came to have a mixture of bluish and yellow colors, and in some of them very considerable sacs of fluid had collected beneath the epidermis. The bullæ soon shrivelled and disappeared, and the cuticle peeled off, leaving dark, bruised pigmentations, which did not disappear for three months. The patient has had a similar experience seven or eight times before. On this occasion the amount taken was only one-half of a grain.

The Gangrenous Form.—In the case above quoted from Briquet, the ecchymotic patch became gangrenous. In one case, reported by Prof. Schuppert, six-grain doses produced an intense localized dermatitis with commencing gangrene of the scrotum. In one of Prof. Kobner's cases, quinine always produced an erysipelas of the scrotum. In several cases, the special tendency to irritation of the skin of the genital parts is noted.

In many of the cases reported, several successive out breaks of the eruption occurred because the physician either repeated the dose without suspecting the causal association of the drug and the skin disease, or did so because he wished to satisfy his own mind as to the patient's susceptibility. The occurrence of one attack seems to confirm and intensify this morbid susceptibility.

It is worthy of note that what may be called the idiosyncratic intolerance of the drug, may be an acquired peculiarity. In a number of cases, my own among them, the patient was previously accustomed to take large doses of quinine without any unusual effects upon the skin. Observations are not wanting which would seem to demonstrate the hereditary character of this peculiar susceptibility in exceptional cases. King reports the case of a lady who had a vivid bright-red efflorescence developed

over the whole surface of the body after taking five grains of quinine. She stated that her father, as well as her sister, were always affected in the same manner after taking quinine. In a number of cases, where preparations of the barks were given, the physician, thinking that the irritant effects might be due to some adulteration, substituted the alkaloid, with a repetition of the same effects. In a majority of the cases, what may be regarded as small doses—one or two grains—were given. The subjects of these observations were mostly females. The greater fineness of the skin and its more exquisite sensibility in women would explain its relatively greater susceptibility to irritant action.

Pathogeny.—One theory of the mechanism of the production of the quinine exanthem is that the drug may act just as irritating articles of food sometimes do, by stimulating the sensory nerves of the gastric mucous membrane, producing reflex dilatation of the cutaneous vessels. While this explanation may apply to the lighter and more transitory forms, such as the erythematous and urticarial, it is manifestly inadequate to cover the severer forms. Another theory is, that the sweat glands have an elective affinity for the drug, and its attempted elimination through this channel causes local irritation. While it is not probable that the drug acts specifically upon any one of the constituent elements of the skin, we can readily understand that it may exert a direct irritant effect through the blood upon the vaso-motor and trophic centres, causing disorders of capillary circulation of which the eruption is but the outgrowth. In purpuric cases, there may be diminished vitality of the cutaneous vessels from disordered innervation, permitting transudation of blood through their weakened walls.

Diagnosis.—The quinine exanthem derives its chief clini-

cal importance from its close resemblance to the rash of scarlatina. This resemblance is rendered more striking from the congestion and swelling of the mucous membrane of the throat and fauces, and the subsequent desquamation, which may be more or less complete, and may last from a few days to several weeks. In one case, reported by Dr. Pfluger, there was exfoliation of the epidermis in large lamellæ, giving a complete cast of the fingers like a glove. When the eruption is accompanied with fever and high temperature, as in the cases of Professor Kobner and two other reporters, its similitude to scarlatina is so perfect as to deceive the most skilful and experienced physicians; but these cases are quite exceptional. The differential diagnosis is usually easy, from the absence of fever and high temperature, the sudden development of the rash, and its rapid subsidence upon the suspension of the medicine. The presence of quinine in the urine, which may be readily detected by simple and easily applied tests, will at once decide the nature of the exanthem.

Tests for Quinine and other Cinchona Alkaloids.

The principal alkaloids of cinchona bark, used in medicine, are quinine, quinidine, cinchonine, and cinchonidine. All of these are eliminated promptly by the urine, without any apparent chemical change. The separation of these alkaloids from the urine is comparatively easy, but their separation from each other, and sometimes their identification, is connected with difficulties, particularly if attempted by inexperienced hands. However, the recognition of quinine and quinidine is comparatively easy. For this purpose, the urine is evaporated to a small bulk, then rendered alkaline with soda, and agitated with chloroform, which will dissolve the quinine, quinidine, and

cinchonidine, and but little cinchonine. (The latter may be subsequently shaken out by a mixture of four volumes of chloroform and one volume of alcohol.) The chloroformic solution is mixed with a few drops of water and evaporated to dryness. A proportion of the residue is then placed on a watch-glass, a few drops of chlorine (or bromine) water poured upon it, and then a drop of water of ammonia, whereupon an emerald-green color will make its appearance if quinine (or quinidine) was present.

Treatment is hardly ever necessary for the cutaneous disorders caused by quinine, since they spontaneously disappear on withdrawal of the offending agent. A simple protective dusting powder will relieve the subjective sensation of heat and itching which commonly characterize the erythematous and urticarial forms.

A number of expedients have been suggested to prevent the irritating effects of quinine upon the skin. Lightfoot observed the rapid disappearance of the quinine eruption following the administration of twenty-five drops of tincture of hyoscyanus and sponging the body with alcohol. Hydrobromic acid, it is claimed, exerts a remarkable influence in counteracting the untoward effects of quinine.

CONIUM.

Conium in large but not toxical doses, according to Stillé, sometimes produces an erythematous or papular eruption upon the skin in conjunction with injection of the eyes, diaphoresis, and other characteristic symptoms.

Dierbach, quoted by Piffard, states that diaphoresis, erysipelatous inflammation, bluish spots, or a rosaceal eruption may follow the internal use of this drug.

COPAIBA AND CUBEBS.

The eruptive disturbances caused by copaiba and cubebs are generally recorded together under the head of "balsamic eruptions."

Since these two drugs are so often given in combination, it would be difficult to differentiate the part played by each in the production of the cutaneous phenomena.

It will be most convenient, therefore, to study their incidental effects upon the skin in the same connection; it must be noted, however, that the two drugs are not equally endowed with exanthematogenic properties: while the eruptions produced by cubebs are quite rare, those which follow the ingestion of copaiba are comparatively frequent. They were first described by Montègre in 1814, and afterward by Ricord, ten years later, under the designation of *érythème des resineux*. Bazin differentiated the clinical features of the balsamic eruptions, and to his admirable description little has since been added.

In some cases, the eruption appears soon after the administration of the drug; in other cases, not until after it has been continued for some days, almost always by the eighth day.

The copaiba rash manifests a predilection for certain regions, as the wrists, ankles, knees, hands, and feet, breast, and abdomen, sometimes it is general, occupying the entire surface of the body. A number of eruptive elements have been met with, but erythema and papules are by far the most common.

The Erythematous and Papular Form.—This is characterized by rosy or bright-red spots, the hyperæmia disappearing on pressure. Its favorite seat of development is around the articulations. The patches are usually

rounded, sometimes irregular, not elevated above the surrounding skin, separated from each other by interspaces of perfectly normal skin, and sometimes coalescing, forming patches of considerable size. Certain observers have described miliary and scarlatina-like eruptions with œdema of the subcutaneous cellular tissue. It is accompanied with itching, which may be very intense. It usually recedes promptly with the cessation of the medicine, the spots gradually fading and disappearing with slight desquamation. If the use of the drug be continued, the hyperæmic spots may develop into papules, or the rash may be papular from the first. Berenguier describes a case of eruption from cubebs, in which the lesions were miliary, but uniting in many places, forming finger-nail sized elevations above the surface of the skin. The eruption spread over the face, arms, and trunk, less abundant over lower extremities. It disappeared with a slight branny desquamation in a few days after stopping the use of the medicine. Weiss gave a young man twenty grains of cubebs, which produced high fever, and an eruption so closely resembling roseola that it was deemed necessary to take suitable precautions to prevent the spread of the infection. The eruption disappeared in three days. A second similar dose produced precisely the same phenomena.

The Urticarial Form.—The rash may commence as an urticaria, or wheals may be developed secondarily upon an erythematous surface. In a case under my observation, the rash on the first day presented the aspect of a roseola affecting only the seats of predilection indicated above. Two days later, the medicine having been continued, almost the entire surface of the body was erythematous and covered with large rosy-red wheals, accompanied with more or less œdema of the face. The eruption was most abundantly developed upon the back, shoulders,

and buttocks. Upon the legs, the eruption was petechial in character. The eruption disappeared with the cessation of the medicine. Two weeks later, the medicine was again given, by way of experiment, with the result of reproducing the same eruptive elements.

The Vesicular Form.—Rayer reports a case in which the administration of copaiba and cubebs was followed by an eruption of vesicles similar to those of eczema. It consisted of numerous pin-head-sized vesicles filled with transparent fluid, developed principally upon the wrists, elbows, ankles, and knees. The skin was red, hot, and swollen, presenting a condition analogous to that of eczema rubrum.

The Bullous Form.—Hardy has reported a case of pemphigus-like eruption following the use of copaiba; the drug first produced an urticarial eruption, discrete upon the face and chest, confluent upon the limbs, attended with intense itching which disappeared in four or five days after the discontinuance of the copaiba. After several days' administration of the drug a second time, there appeared an eruption of large, irregular, incomplete bullæ, which readily ruptured, followed by desquamation lasting six weeks. The eruption came out in successive crops—the duration of each bulla was about six days.

In 1874 I was called to a patient who had been taking copaiba, whose entire body was covered with a patchy erythematous eruption, very itchy; the spots were discrete except around the ankles, in which location there was a belt of vivid diffuse redness two or three inches in width, completely encircling them; over this reddened zone there were a large number of bullæ, some of them discrete, others confluent. The development of the bullæ in this locality was attributed to the pressure of elastic gaiters.

The petechial form of copaiba eruption is usually asso-

ciated with the erythematous and urticarial. Hyde has seen the rash of copaiba occur in dark mulberry red patches. Judd describes a copaiba eruption resembling the bite of insects.

Mauriac describes an eruption from copaiba and cubebs presenting unusual features. After the eruption had lasted several days, the spots upon the extremities, especially upon the forearm and wrists, displayed centres of ecchymotic redness surrounded by pale-red circles, which in their turn were circled in other circles of dark red, each patch measuring from two to three centimetres in diameter. On the lower extremities there were multitudes of pin-head-sized petechiæ.

Diagnosis.—The copaiba rash derives its chief clinical importance from its similarity to the erythematous syphilide and the rash of the eruptive fevers, especially rötheln, when the papular element predominates. The diagnostic differences in configuration, color, localization, exhalation of resinous odor of the drug, etc., need only be alluded to. The odor of the essential oil of copaiba, of cubebs, of juniper, and of turpentine (pure) can generally be distinguished. This may, however, be done with greater certainty if the urine is distilled to a syrupy consistence, and the distillate shaken with petroleum ether of as low boiling point as possible (f. i., rhigolene). On spontaneous evaporation of the latter, the odor of the essential oil may usually be recognized, when the last traces of the solvent are volatilized. If this moment is missed, the essential oil itself may volatilize and thereby fail to be identified.

DIGITALIS.

The external application of the fresh leaves of foxglove in the form of an ointment excites an irritation of the skin which may result in an erythema, or an eruption papular in character. The production of an exanthem from the ingestion of digitalis has been but seldom observed. Behrend, quoted by Hyde, refers to macular and maculo-papular eruptions succeeding its use.

Traube reports two cases in which affections of the skin resulted from the internal use of digitalis. In one case, the patient had taken a quantity of the infusion representing nearly sixty grains in the course of two days. Four days after the last dose, there appeared an erysipelatoid affection of the face, which terminated in an excessive ragged desquamation a few days later.

In the next case, sixty-one grains had been taken in the form of an infusion in the course of five days. Four or five days after the last dose, an eruption of prominent reddish papules appeared on the body, backs of hands, and forearms. These papules coalesced, forming large patches elevated above the surface of the skin. The next day, new patches appeared upon the upper arms and neck. The exanthem disappeared in a few days, desquamation in large flakes occurred some days later on the body and extremities.

It is a noteworthy fact that the eruption appeared in each case four days after the suspension of the medicine, which is in harmony with the well-known cumulative effects of the drug upon other organs when not rapidly eliminated from the vascular channels.

Schuchardt reports a case where a similar form of

eruptive disturbance, involving the entire surface of the body, was twice developed by the use of digitalis.

A case in which the irritant action of digitalis upon the skin was singularly shown, came under my observation a few years ago. The patient had been taking infusion of digitalis in active doses, with acetate of potash, for partial suppression of the urine. After a few days of this medication, there appeared an erythematous efflorescence over the entire surface of the body, which the family of the patient thought was scarlet fever. The next day, the medicine still being continued, the whole surface was covered with an urticarial eruption. The wheals appeared as large prominent plaques, elevated considerably above the surface, and intensely itchy. There was œdema of the face, puffiness of the eyelids, high temperature, and considerable constitutional disturbance. The eruption began to disappear in the course of two or three days after cessation of the medicine. Desquamation in large flakes continued for several weeks. There was complete alopecia of the scalp and shedding of the nails of the fingers and the toes. Albuminuria was constantly present for some time after the attack.

DULCAMARA.

The most characteristic incidental effect upon the skin produced by the ingestion of this drug is an increased sensitiveness, and the appearance of an erythematous condition. Urticarial and "red-scaly" eruptions have also been recorded from its use.

ERGOT.

The condition called "ergotism" may result from the internal administration of the drug in medicinal doses, or from the consumption of bread or other farinaceous food strongly impregnated with the diseased rye. Changes in the skin from the ingestion of ergot are comparatively rare, and only supervene upon its long-continued use. A vesicular eruption upon the skin with petechiæ has been observed, also a pustular and furuncular inflammation; sphacelus and circumscribed gangrene may occur on parts distant from the centres of circulation.

The group of skin lesions comprehended under convulsive and gangrenous ergotism will not be considered here, since they are phenomena caused by consumption of food infected with ergot, and rarely result from the use of the drug in medicinal doses.

The hypodermic injection of ergotin is usually followed by more or less intense symptoms of local reaction. At the point of puncture there generally results a painful black unsightly swelling. These nodules are exceedingly sensitive, and may persist for some time. A phlegmonous inflammation around the point of injection not infrequently results. Carrying the instrument deep down into the subcutaneous tissues does not prevent the formation of these nodular infiltrations.

FERRUM. IODIDE OF IRON.

The most common cutaneous disturbance observed from the internal use of iron is an acneiform eruption. Trousseau says that it is more frequently observed in women, and is developed upon the face, breast, and back, without constitutional disturbance.

Of the various salts of iron, the iodide is the only one commonly credited with the power of producing well-marked irritative effects upon the skin. The eruptions which may follow the ingestion of iodide of iron have been described as "erythematous," "papular or urticarial," "eczematous," and "pustular" in character. Since these irritant effects are most probably due to the iodine contained in the preparation, they will more properly be considered under the head of eruptions produced by iodine and its compounds.

HYDRARGYRUM. MERCURY.

The application of mercury to the skin, as in the form of unguentum hydrargyri, occasions, as is well known, various degrees of irritation. The grade and extent of the inflammatory action will depend upon the strength of the preparation used and the duration of its contact. This may vary from a slight erythema to a high degree of dermatitis, and the formation of sloughs. The most common form is an erythematous or vesicular eruption. The vesicles are usually small, closely aggregated, and frequently develop into pustules, especially when seated around the hair follicles.

The local application of corrosive sublimate in the form of antiseptic dressings, which is practised by so many surgeons at the present day, has been followed by eruptive

disturbances in a large number of cases. Dr. Reichel reports the following case: After an operation for genu valgum, the leg, from foot to pubes, was enveloped in the sublimate gauze. On the fifth day, sensations of burning and itching were felt in the limb. Upon removal of the bandages, the leg was found to be covered with an intense papulo-vesicular eczema; the integument was œdematous. A general erythema was now developed; the whole body, except face and neck, was thickly covered with small, red spots, especially upon the breast, abdomen, scrotum, and back of elbows. Four days after the removal of the sublimate bandage, the eruption disappeared. Numerous other cases of eczema mercuriale have been reported from the use of the sublimate dressing. Netzel reports a case of erythematous eruption about the pelvis, and extending over the body, resulting from the use of sublimate injections after confinement. Lessona observed at the Maternity Hospital at Turin three cases in which a peculiar roseolous rash followed the use of sublimate injections after child-birth. The rash first appeared upon the breasts, and was preceded or followed by salivation.

The fact that eruptive disturbances sometimes follow the ingestion of mercurial preparations was recognized by Benjamin Bell in 1796, who first described eczema mercuriale. In a monograph published in 1804, Alley grouped under the general term Hydrargyria several forms of eruption which he described as H. mitis, H. febrilis, and H. maligna.

1. *Hydrargyria mitis.*—The eruption consists of a slight efflorescence localized in certain regions, such as the internal surface of the thighs, scrotum, the groin, and the lower segment of the abdomen, sometimes, but rarely, on the arms, back, and face. A close examination of these

reddish patches reveals a multitude of minute vesicles filled with a transparent fluid. It is attended with intense itching, but the eruption usually subsides soon after the cessation of the medicine.

2. *Hydrargyria febrilis.*—This form may develop *ab initio*, or, as is more frequent, it succeeds the benign form, and manifests itself as a more severe inflammation of the skin. There is an intense scarlatiniform redness occupying the entire surface. Upon this appear, towards the fourth day, larger and more voluminous vesicles, coppery in tint, distended with a purulent fluid. These vesicles rupture and crust over, resembling the crusts of eczema. There is considerable fever and constitutional disturbance. Desquamation occurs in flakes, as in scarlet fever. Sometimes several successive exfoliations take place.

3. *Hydrargyria maligna.*—The phenomena of this stage are simply an aggravation or intensification of the preceding from a continuance of the drug after the vesicular eruption has declared itself. The skin becomes of a purplish-red hue, swollen and painful, and is covered with confluent vesicles or large bullæ filled with a sero-purulent fluid. The constitutional disturbance is correspondingly increased with the aggravation of the cutaneous symptoms; desquamation takes place from the fourth to the eighth day, the epidermis peeling off in large flakes.

Small doses of the drug are capable of exciting an irritant action upon the cutaneous system. Alley saw it in one case after taking two grains of calomel, and in another case, after three grains of calomel. Fournier, cited by Hallopeau, observed an eruption identical with that of scarlatina, which appeared on the face, trunk, and extremities of a patient who had taken five centigrams of protiodide of mercury. It was followed by a desquamation even more abundant than is observed after ordinary

scarlatina. The same scarlatiniform eruption, followed by abundant desquamation, occurred after the use of acid nitrate of mercury and Dupuytren's pills.

Engleman reports a case of desquamative erythema after taking three doses, two and one-half grains each, of calomel. The eruption first appeared on the head, with œdema of the face, and in one night spread over the whole body; the patient had had similar experiences after taking mercurial pills, and also after having been exposed to mercurial vapors.

Blanchon reports a case of a woman exposed to fumes of mercurial vapor. After five or six days, a roseolar eruption first appeared on face and neck, and became generalized. On certain parts, as arms and upper part of trunk, there were figured and crescentic patches on a slightly reddened base, as seen in morbilliform erythemas. The eruption, which was not attended with constitutional disturbance, disappeared in five or six days.

Almost every form of eruptive disturbance has been recorded as occurring from the internal administration of mercury; urticaria, herpes, impetigo, purpura, furuncles, with ulcerative lesions involving considerable loss of tissue.

Tests for Mercury.

The most certain method of detecting mercury in the urine is by electrolysis, that is, by causing it to be deposited, in a metallic state, upon either gold or copper (or certain other metals), and then examining the deposit for its identity.

Take a piece of bright gold-wire (or some other smooth article of gold), wind about it, in a spiral form, a piece of bright iron-wire, and immerse the whole into the urine, slightly acidulated with hydrochloric acid. Any mercury

present will be deposited partly on the gold, partly on the iron.

Or, dip into the acidulated urine a piece of bright copper-foil, with a piece of zinc-wire wound about the upper part. In this case, the mercury will deposited on the copper.

The next step is to identify the deposit as mercury. For this purpose, introduce the amalgamated metal into a glass-tube closed at one end, and heat it. The mercury will become volatilized and be deposited in the cool part of the tube. The deposit may be distinguished from the similar one produced by arsenic and antimony by its not being oxidized to white compounds (oxides) when it is heated with access of air, and further by the fact that it is not rendered yellow or orange by hydrosulphuric acid, but black, which color is, however, only superficial. Sulphide of ammonium converts it completely into black sulphide of mercury.

HYOSCYAMUS.

Although the physiological action of hyoscyamus so closely resembles that of belladonna and stramonium, yet its irritant action upon the skin is less strongly pronounced than that of the two other drugs, and the eruption is less vivid in color.

The most common form of eruption produced by the internal use of hyoscyamus is erythematous. The congestion of the skin is usually preceded by burning and itching, and attended with more or less œdema, sometimes with the production of urticarial wheals.

White describes a case in which there were burning and pricking sensations in the hands, feet, and legs, and a generalized purplish rash, especially upon the face and neck, with great swelling of the parts. Craik reports the

occurrence of a red rash-like scarlatinal eruption in a child caused by eating the leaves of the hyoscyamus.

Bessières reports a case in which the patient was accustomed to use vaginal injections of a decoction of hyoscyamus, but suffered from an erythematous eruption after the same injection per rectum.

Pustular as well as purpuric eruptions have several times been observed from the repeated internal use of small doses of henbane.

IODINE. IODIDE OF POTASSIUM. IODIDE OF AMMONIUM. IODIDE OF SODIUM, ETC.

The iodic eruptions include all changes in the skin caused by the alkaline iodine salts. All of the various compounds of iodine are capable of producing disorders of the cutaneous system; but, since the drug is usually administered in the form of iodide of potassium, the eruptions recorded under this head may be regarded as representative of the whole class. The eruptive disturbances connected with the use of iodoform will be considered separately.

The local action of iodine, either in the form of the tincture or vapor upon the healthy human skin, is well known. The skin is first stained yellow and then assumes a brownish-red color. The epidermis is shrivelled and loosened from its attachment, and desquamates in flakes. This process is attended with burning, itching, and more or less pain. The effects are not limited to the point of application, but may be manifest on different parts of the body in the shape of papular, pustular, or even bullous eruptions. These irritative effects upon remote portions of the body are most frequently observed after repeated applications of the tincture, and are probably consecutive

to absorption of the drug. It has been observed that erythematous patches have appeared upon the body after the injection of an ovarian cyst with tincture of iodine. Similar effects have followed the injection of the tunica vaginalis after tapping for hydrocele. Simon and Regnard observed after the application of tincture of iodine with glycerin to the eczematous scalps of children an extensive papular eruption on the face and other parts of the body.

The occurrence of cutaneous disturbances from the ingestion of iodide of potassium have been recognized since its introduction into the materia medica, although certain rare and somewhat singular effects upon the skin have not been recorded until within a few years past.

The literature of iodic eruptions, comprising almost innumerable observations relating to all forms of cutaneous disorders, from simple erythema to the severest forms of dermatitis, attended with severe constitutional reaction is so vast that its mere enumeration would require several pages.

Fischer, who, as early as 1859, made a special study of iodic eruptions, divides them into four principal forms, the erythematous, the urticarial, the nodulo-pustular, and the eczematous. Since then, with the widening of our knowledge of the range of pathogenetic action of this drug, new eruptive elements have been recognized. Fournier, though by no means the first to describe the petechial form, has traced its clinical characters with precision. The bullous form, first described by O'Reilly, of New York, has been carefully studied by Bumstead and others.

Quite recently Celso Pellizari has reported two very rare cases in which there were large inflammatory nodular masses, varying in size from that of a nut to the size of the fist, seated in the subcutaneous cellular tissue, accompanied by high fever, followed by abscesses which healed slowly

and left cicatrices. Besnier has still more recently called attention to a carbuncular eruption, under the designation of eruption anthracoide iodo-potassique.

The iodic eruptions may be classed according to their elementary lesions, as follows:

The Erythematous Form.—This usually occurs on forearms, face, and anterior surface of the chest. The redness may be diffuse, or appear in discrete and irregular spots or in large circumscribed patches; exceptionally it may extend over the whole surface of the body. This hyperæmia may be intensified and developed into

The Papular and Urticarial Form.—There may appear upon reddish patches, or upon the skin uniformly congested, intensely red, slightly-raised papules, which are frequently grouped. In some cases, the larger papules are surrounded by an areola. The eruption is principally developed upon the hypogastrium and the extremities, but may be general. The papules have a certain analogy with an ordinary urticaria, from which they differ by their exaggerated development, their brighter coloration, generally described as rose red, and which becomes pale on pressure. Besides the difference of color, there is sometimes seen, as in a case of Pellizari's, a kind of telangiectasic condition suggesting nævus maternus.

Pellizari has more recently presented a report of several cases of iodic eruption in which the characteristic features were those of urticaria and papular erythema. In one case the urticarial nodules became converted in phlyctenulæ, containing sanguinolent pus. Large ecthymatous pustules, anthracoid acne, nodules of variable form, and numerous superficial abscesses were also present, constituting a polymorphous eruption.

Taylor recently brought before the New York Dermatological Society a patient in whom an urticarial eruption

had been developed twice by a few fifteen-grain doses of the iodide of potassium. The eruption was confined to the face, neck, backs of hands and wrists. Many of the wheals were surmounted, on the second day of the eruption, by pellucid vesicles.

The Vesicular Form may also develop from the erythematous. Berenguier describes a scarlatiniform rash of sudden occurrence upon the chest and limbs, upon the surface of which were numerous small, discrete vesicles. Mercier reports a case of an iodic eruption resembling eczema rubrum, accompanied with severe fever, and characterized by an extremely copious exudation of fluid. The same eruption was reproduced in the same individual in both instances by moderate doses. An eczematous form, which is said to be very rare, develops especially on the hairy scalp, and in the neighborhood of the scrotum.

The Bullous Form.—Comparatively few cases of bullous eruption caused by the ingestion of iodide of potassium are found recorded in the literature of drug eruptions, and it may therefore be classed among the rarer cutaneous manifestations of the drug. A most remarkable case of this eruptive form recently came under my observation at Charity Hospital.

The patient, Albert Stout, a German, about fifty years of age, had been taking a solution of iodide of potassium (1 in 2), ℥ i. t. i. d. Three or four days after beginning the use of the medicine, there was observed an erythematous condition of the face, with the production of vesicopustules about the size of a pea. Under the continued influence of the drug, the dermatitis increased in intensity and severity, and the vesicles developed into bullæ of varying size. The iodide was discontinued after ten days' treatment, when he had taken nine hundred grains altogether. He was then given sulphide of calcium, one-fifth

grain three times a day for three days, when he was transferred to the Dermatological Ward, October 9th, 1885. Upon admission, the entire face, the ears, and the neck down to the level of the hyoid bone were found to be the seat of an eruption, also the dorsal surfaces of hands and wrists. The integument of the forehead and face was bright-red, and infiltrated to such a degree as to be a quarter of an inch thicker than normal, causing the natural lines of the skin to appear like deep furrows. The skin appeared as if thrown up into prominent bosses or ridges, separated by intervening depressions. The enormous tumefaction of the supra-orbital folds gave a leonine appearance to the face. The eyes were closed from the œdematous condition of the upper and lower lids.

The face, and especially the forehead, was thickly studded with small vesico-pustules, many of which had broken, leaving a mass of crusts. Upon the upper portion of the forehead, the fusion of the closely-crowded bullæ had formed a belt or zone of raised epidermis, simulating in appearance the advancing border of an erysipelatous inflammation, which stopped abruptly at the line where the hair began. The dermatitis, both of the face and posterior portion of the neck, did not encroach upon the hairy scalp. The swollen alæ of the nose were covered with a number of pea-sized lesions, some of which had become pustular. The ears were greatly swollen, and where the crusts from ruptured bullæ had been picked off by the patient, bloody crusts were to be seen. The skin became pale on pressure, but did not pit, and immediately resumed its red color when the finger was withdrawn.

Upon the dorsal surface of the hands and wrists, the skin was reddened and infiltrated, though not to the same degree as upon the face. On the dorsum of the left hand, from the wrists to the tips of the fingers, were a number

of bullæ varying in size from a three-cent piece to that of a silver dollar.

Upon the right forearm above the wrist, there was one large bulla and two smaller ones, with a few vesico-pustules. The back of this hand was occupied by a large bulla, the size of a pigeon's egg, surrounded by a number of smaller ones, suggesting in their arrangement a magnified herpes iris; toward the ulnar or outer border were four or five bullæ, ranging in size from a large pea to that of a cherry; the second, third, and little fingers were occupied by bullæ extending along their entire length to the tips, the walls tensely distended with a sero-sanguinolent secretion. Both hands presented a swollen, puffy appearance. There was no eruption upon any other portion of the body. Examination of the mouth and fauces revealed nothing beyond an intense congestion of the mucous membrane. The patient was in a state of profound prostration; he was dull and stupid, and could be aroused with difficulty: there was more or less tremor of the hands, and he was constantly moving them toward his face. His respiration was quickened and his pulse was 120, temperature not taken.

Oct. 10th. The general appearance of the face was about the same as yesterday. The bullæ upon one hand had become coherent at their bases, but did not coalesce. Upon the other hand, the lesions had become confluent, forming an enormous bleb, extending from the annular ligament of the wrist to the tips of the fingers. The color was a steely blue, bearing a striking resemblance to the appearance of a coil of intestine. The general condition of the patient unchanged; resp. 23, pulse 112. Catheter will not pass on account of stricture at four and a half inches, admitting No. 10 sound with difficulty. Urine duck kept in bed with patient. He was placed upon an

extra diet, and ordered whiskey, ℥ iv. per diem. The face and hands to be dressed with carbolized vaseline. Some of the bullæ were punctured, yielding a reddish serum which was examined for iodine with negative results.

Oct. 11. No change in appearance except that some of the older bullæ on hands have become dirty-blue in color, and on puncture give exit to a dirty-red sero-pus instead of a clear serum as before. Examination of heart showed a systolic apex murmur transmitted towards left axilla. Diagnosis of mitral insufficiency. Temperature, 100.1°; resp., 22; pulse, 114.

Oct. 12. Infiltration of the skin has subsided somewhat; examination of the urine shows it acid in reaction, sp. gr. 1.010, with a considerable amount of albumin, 10 to 15 per cent. Under the microscope a few pus and blood globules are seen; no casts.

Oct. 14. On the back of the neck the skin has returned to its normal level, but is still red, the face less swollen, eyes well open and bright in appearance, leonine appearance of countenance gone. The bullæ on hand present a blue-black coloration. A bloody pus, slightly offensive, comes from one or two ruptured bullæ. All the bullæ were ordered to be cut open, washed out with 2½-per-cent carbolic solution, and dressed with carbolized vaseline. The floor of some of the bullæ is bathed in pus, apparently due to superficial ulceration.

Oct. 21. Continued improvement in general condition of patient, the backs of the hands cleared off and presenting a healthy appearance.

Oct. 29. The skin of the neck and a good part of the face has returned to its normal condition, though still somewhat hyperæmic. Raw surfaces on dorsum of hands and fingers healing.

Nov. 5. Almost all traces of the eruption gone, though

no gain in the patient's general condition. Patient has cough. Examination of chest shows dulness at apices of both lungs, with increased fremitus, prolonged high respiratory murmur, and few moist râles. Passes urine and fæces in bed as on entrance.

Nov. 15. Patient has continued to fail. Increasing frequency and feebleness of pulse (120); resp. 32. Examination of chest shows pulmonary œdema.

Nov. 16. Patient died quietly at 2 P.M.

Autopsy showed *heart* enlarged and dilated on left side. Insufficiency of mitral valve and atheromatous deposits. Aorta atheromatous. *Lungs* œdematous; phthisical consolidation at both apices; no cavities. *Kidneys* somewhat diminished in size and heightened in color; consistence increased; surface granular; capsule adherent. *Liver* and *spleen* normal.

The drawing representing the face in the picture (vide Frontispiece) was made on the second day after the admission of the patient, when the more acute eruptive features had begun to subside. The direct dependence of the eruption upon the iodide of potassium in this case would seem to be conclusively established; first, by the appearance of the cutaneous phenomena within three or four days after commencing the use of the drug; second, by the intensification of all the eruptive features under its continued use; third, by the subsidence of the eruption soon after the drug was withdrawn, and, fourth, negatively, by the absence of any other known exciting cause.

In this case the eruption did not attain its maximum development until four or five days after the iodide was discontinued. Whether the sulphide of calcium, given in the interim, exerted any material influence in intensifying and perpetuating the eruptive tendency, is open to question.

The comparatively slow involution of the lesions was probably due to the profound systemic depression caused by the drug, and the existence of the grave organic troubles which ultimately proved fatal.

As early as 1842, Ricord refers to a rupia-like eruption, presenting the characters of a cachectic rupia, which he had observed upon the forearms and legs of a patient who was taking iodide of potassium. The eruption disappeared upon discontinuing the drug, and reappeared when its use was resumed. While this eruption was probably closely allied, if not identical, with that under consideration, its clinical characters were not traced with sufficient precision to justify its inclusion under this category. The first authentic case of bullous eruption caused by iodide of potassium was reported by Dr. John O'Reilly in the New York *Medical Gazette*, January, 1854.

The special features which characterize this eruption are the development of bullæ of varying size, often commingled with vesicles and small pustules. The lesions usually make their appearance as vesicles or vesico-pustules which rapidly increase in size, forming regularly rounded or globular bullæ from the size of a pea to that of a pigeon's egg, or even larger; they may remain discrete, or coalesce with neighboring bullæ; in which case they may attain enormous dimensions. In other cases they begin as hard papules, the shot-like character of the papules suggesting the commencing stage of variola. This resemblance is heightened by the rapid transformation of the papules into vesicles, and their tendency to umbilication, which is quite manifest in some cases. There is generally more or less thickening or infiltration of the skin, and the lesions may be surrounded by an inflammatory areola, variously described as "erythematous," "bright-red," or "a dark wine color." In some cases the epidermis is up-

lifted without inflammatory swelling of the skin, presenting the appearance of a blister produced by a burn. In one case the eruption was described as "an eruption of blisters, compared to "potato apples," each blister surrounded by a series of bright-red concentric rings.

In a number of the cases, there was a coëxistence of renal and cardiac complications which may explain the comparatively large fatality observed. We can readily understand why defective elimination of the drug should act as a co-factor in the causation of cutaneous irritation. The greater part of the iodine is normally eliminated by the kidneys within twenty-four hours after its ingestion; when this channel of egress is blocked up, the drug is longer retained in the vascular channels, and exerts its irritant action upon the tissues. But why cardiac disorders should produce a morbid determination of the drug's action towards the cutaneous system is not so evident. Thin has suggested that this may be due to the feeble heart impulse and consequent sluggish circulation in the cutaneous capillaries, allowing the iodine or its compounds present in the blood time to attack and injure parts of the vascular wall. It is needless to say that the retarded elimination of the drug does not explain the occasional occurrence of the eruption within a few hours after the ingestion of a single insignificant dose.

The Papulo-pustular Form.—This may be regarded as typical, as it is the most common, of the eruptions provoked by the action of the iodides. It presents certain analogies with the acneiform eruption produced by the bromides. It usually appears upon the face, backs of shoulders, upper part of chest and arms, where the sebaceous glands are abundant. Sometimes, however, it surpasses these limits and is found distributed over a large surface of the body. The eruption commences as hard, shotty pap-

ules, which usually enlarge and become surmounted by small pustules, when fully developed. The iodic pustules may be described as consisting of acuminated or rounded eminences, more or less voluminous, with a reddened, somewhat infiltrated base, suppurating sometimes only at the summit, at other times in the totality of the pustule. The contents of the pustule concrete into a yellowish crust, which may persist for some time, and on falling leave a distinct cicatrix. Sometimes the tubercles, instead of ulcerating, become transformed into nodules of firmer consistence, intensely red, deeply seated in the tissues, which are remarkably slow in their involution.

The Anthracoid Form.—In this connection may be described an eruption of carbuncular lesions which resembles the "confluent acne" produced by the bromides. Besnier designates it as *acné anthracoide iodo-potassique.* In his two cases, the face and thorax were covered with veritable tumors of variable volume, of a reddish coppery hue, flabby, almost fungous, and presenting punctate depressions or vacuoles analogous to those of anthracoid furuncle. It was impossible to express their contents; incision gave exit only to blood. In Duhring's case, there was a confluence of the nodules, forming a sharply defined, rounded inflammatory patch, violaceous in color, its centre depressed and crusted, while the periphery was studded with numerous deep-seated, yellowish, sebaceous-looking pustules presenting an acneiform appearance. When cut into, the yellowish pustular points bled, but did not exude their contents. When the crust was lifted from the central lesion, it showed a red, glistening, firmly mammillated or warty surface. There were four of these lesions occupying the forehead, cheeks, and nose. The one on the forehead was two inches in diameter. In a case of Dr. Costa's referred to by Atkinson, the lesions were situated upon

the back and chest, as well as the face. The suppression of the medicine was followed in all of these cases by the involution of the lesions in about two weeks, some of them leaving a brownish macule, with cicatricial depression.

The Petechial Form.—Although Ricord, as early as 1842, mentioned among the eruptions produced by the iodide of potassium the occurrence of "petechiæ resembling the spots of the morbus maculosus Werlhofii—a veritable purpura hemorrhagica," Fournier was the first to carefully study the purpuric eruption. He describes the lesions as discrete, miliary, millet-seed to lentil-sized spots, usually rounded, more rarely oval or discoid in form. Its seat of predilection is the legs, more especially the middle three-fifths, avoiding the knees and feet, and developed more profusely on the anterior than the posterior surfaces. Ordinarily there are as many as one hundred discrete spots on each leg. Petitjean describes a case in which the eruption appeared on the dorsal surface of the feet, and another observer saw it upon the forearms and wrists.

According to Fournier, the explosion of the petechial accidents almost invariably occurs soon after the commencement of the treatment, usually in from one to three days. The eruption reaches its height in two or three days, and, if the medicine be discontinued, disappears in the course of two or three weeks. In certain persons, the same eruption may occur several times after each new use of the iodide. In the course of a continuous treatment, each notable elevation of the dose was followed by a marked recrudescence or a new crop of purpura ("*une poussée subintrante*"), contrasted by their vivid coloration with the faded earlier eruption.

Fournier regards the eruption as rare, as he had observed it only in fifteen cases. I have seen several cases. In one

old lady, I redeveloped the eruption four different times, in order to test its causal connection with the iodine. She had been taking the medicine some time in small doses when my attention was called to the eruption. Each time thereafter it was reproduced within forty-eight hours by the use of five-grain doses of the iodide. McKenzie reports a remarkable case of iodic purpura in a child, caused by a single dose of two and one-half grains. The case terminated fatally.

It has been suggested that iodic purpura is more apt to occur in anæmic, debilitated persons who have taken the drug for some time. This view has not been confirmed by my own experience, nor that of many others. Fournier emphasizes the statement that an anæmic condition or syphilitic cachexia could not be regarded as a predisposing cause. Two-thirds of his patients were absolutely exempt from every manifestation of syphilis at the time when the iodide, given as a preventive of further accidents, determined the eruption.

Nodular Form.—Vallanur reports a case in which a woman, after taking two and one-half grams of the iodide for four days, was attacked with acute pains in the buttocks, thighs, calf of the leg, and dorsal region; then there appeared upon the painful points small indurated nodules of the size of a nut, of a deep red color. During three days, they increased in size, one or two attaining the size of an egg. The iodide was discontinued, and the nodosities rapidly disappeared. Some days later, the iodide was again administered and the same cutaneous accidents were reproduced. This experiment was repeated three times, always giving the same results.

Talamon reports the case of a woman in whom two and one-half grams of iodide of potassium produced an eruption resembling erythema nodosum. There were at

least twenty red and indurated nodules situated upon the lower limbs, the loins, and buttocks. The lesions were made to reappear at three different times by the use of the iodide.

Hallopeau observed the development of painful nodes in one of his patients, which was repeated every time he took the iodide of potassium. The tumors were oval in shape, reddish at the surface, and painful on pressure; they were situated chiefly on the anterior surface of the thighs. In conjunction with the nodular eruption, the patient also had iodic purpura.

Polymorphous Eruptions.—While the particular form in which the iodic eruption is manifested in different persons is, as a rule, unique and determined principally by the constitutional reaction of the individual, yet it sometimes happens that a combination or association of different eruptive elements is met with in the same individual; we have seen above that papules, tubercles, and pustules may co-exist in the papulo-pustular form, the papule representing the first stage of the morbid process, of which the pustule is the acme or completion. Ecthymatous pustules and furuncles may begin as hard papules, nodules may suppurate and follow all the evolutions of a subcutaneous abscess, the successive stages representing different forms of lesions.

I recently presented a case before the New York Dermatological Society in which ten-grain doses of iodide of potassium developed a polymorphous eruption, preceded by intense lachrymation, coryza, and œdema of the face and eyes. The whole of the nose presented on the third day of the eruption a red, fungoid appearance, being greatly enlarged. The forehead, face, neck, and forearms were also the seat of the eruption. On the left cheek was seen a furuncle; over the malar bone, a large, dark bulla;

on the forehead were many papules and pustules. The eruption on the back of the neck very much resembled molluscum contagiosum. On the forearms, there was a variety of eruptive elements--papules, tubercles, vesicles, pustules, and bullæ.

In a case reported by Celso Pellizari, three eruptive forms of an entirely different character were present at the same time, viz.: on the left forearm near the wrist, there were three slightly elevated papules, the size of a cent, with a rough surface and dark strawberry color. Upon the arms and legs were eight or ten eruptive elements, about one-half inch in diameter, similar to the bullæ of rupia, surrounded by a circumscribed dark-red areola; and on the top, there was a bulla like that produced by a burn, altogether different in character from the cachectic or syphilitic form; the third form was represented by three tumors, from the size of a nut to that of a small apple, deeply seated in the subcutaneous tissue. On stopping the iodide, the papules quickly disappeared; the bullæ dried up, leaving scars which soon became white; the nodules disappeared more or less quickly, according to their size. The eruption was redeveloped in this case several times by the renewal of the iodide, each time accompanied by a high temperature, etc.

The distinguishing characteristics of iodic eruptions are their multiformity, their frequent occurrence after small doses of the drug, their usual prompt disappearance after its use is suspended, their frequent association with its well-known physiological, as well as incidental abnormal, effects upon other organs, their proneness to develop in connection with cardiac and renal disorders. Though usually of transient duration and insignificant import, they may be attended with the gravest symptoms, and exceptionally may lead to a fatal termination.

The length of time which intervenes between the administration of the drug and the first appearance of the eruption varies according to the size of the dose and the predisposition of the individual; usually it is from the third to the sixth day. This period may be reduced to a few hours, or lengthened to several weeks; in general it may be said that, while it may require several days to develop the eruption the first time; after its disappearance, a single, small dose may suffice to redevelop it in the course of three or four hours. A half-grain of iodide of potassium has been known to reproduce an urticarial eruption developed in the first instance by five-grain doses. In case reported by Duffy, the patient had taken the iodide for over a month, thirty grains a day at first, afterwards sixty grains per day—two and one-half ounces in all—before the eruption appeared. It was redeveloped by forty-five grains in one day. Exceptionally the eruption may continue to come out after stoppage of the drug. In Besnier's case, a bullous eruption was first developed by two grams, the second time by one gram, and the third time by ten centigrams. There seems to be no definite relation between the size of the dose and the form of the eruption; this would appear to be a matter of individual constitution. The acneiform eruptions have been more often observed after protracted use of the drug, while the bullous and petechial forms have shown themselves more promptly. The exceptions which have been noted to this rule, however, prove that the determination of the different varieties is independent of the mere fact of chronicity of treatment.

The cutaneous phenomena caused by the internal administration of iodide of potassium are undoubtedly due to the contained iodine, and *à priori* we should conclude that identical effects would follow the use of all the iodine

compounds, especially the alkaline salts. It has been affirmed, however, that the different salts exert this irritative influence in different degrees of intensity, the iodide of ammonium representing the highest degree of pathogenetic power, the iodide of potassium the next, and the iodide of sodium the least. It must be admitted that the observations upon which this comparative estimate is based are too few in number to justify conclusions possessing scientific value. In Duffy's case, iodide of sodium was given in ten-grain doses three times a day for eight days, with failure to reproduce an eruption of "iodic purpura" which had previously been twice developed by iodide of potassium. Iodide of ammonium being then substituted, two doses, twenty grains, brought out the eruption within twelve hours. In a case reported by Ringer, thirty grains of iodide of potassium for five days developed a pustular eruption, which disappeared within a few days after stoppage of the drug. The eruption was redeveloped by the same treatment, to again disappear when the medicine was discontinued. The iodide of ammonium was now ordered in ten-grain doses three times a day, and the eruption appeared after the second dose. The iodide of sodium was then substituted in the same doses and continued for four days, but without bringing out the eruption, which, however, promptly reappeared after a single dose of iodide of ammonium.

Pathogeny.—The first requisite for a clear understanding of the pathogeny of iodic eruptions is the determination of the anatomical seat of the lesions. It was formerly believed that the sebaceous glands constituted the points of departure of all iodic eruptions, but it is hardly probable that eruptive elements so dissimilar as pustules, petechiæ, and bullæ, etc., should have a common starting-point. Their very multiformity constitutes a fatal objection to

such an assumption. It is well known that iodine, while principally eliminated by the kidneys, has been found in the saliva, sweat, and other physiological secretions. Adamkiewitz claims to have demonstrated its presence in the pustules of iodic acne, and therefore concluded that the sebaceous glands secrete iodide of potassium. He believes that the iodide undergoes a chemical modification by contact with the contents of the sebaceous glands, forming irritating compounds. Fox asserts that the iodic lesions are situated in the follicles and are due to excessive stimulation of the sebaceous structure consequent upon elimination of the drug through this channel. The bullous form and other unusual and severe phases of the eruption he regards as exaggerated acneiform lesions, with excessive and altered secretion of sebum.

This view is opposed by other authorities, who go so far as to deny the existence even of iodic acne. Duckworth says that the glands are not the seat of pustular acne, and records a case in which the same eruptive form appeared in cicatricial tissue, where probably no glands remained. Other observers have noted its occurrence on the palms, where the presence of sebaceous glands has never been demonstrated. Thin, who rejects the theory that iodine eruptions are produced by stimulating effects on the secreting elements of the sebaceous glands, believes that all the varieties of the eruption may be explained by the tendency of iodine, when present in the blood current, to attack and disorganize the vessels at special points. "The injury in its mildest form is seen in common iodic acne, in more severe forms in the bullous and pustular eruptions, and in the worst form in iodic purpura. In the first we have limited œdema with congestion of the vessels; in the second, an effusion of serum with more or less of the formed elements of the blood; in the third, destruction of the wall of the

vessel and hemorrhage." In the explanation of the severer forms he suggests that a sluggish circulation and deficient excretion may find a place.

In his microscopic examination of a bulla produced by iodine, he found that the lesion was formed by injury to the walls of the blood-vessels of a limited area and by consequent escape of blood, which displaced the connective tissue, pierced the rete mucosum, and accumulated under the horny layer of the epidermis. That this injury to the blood-vessels is independent of the glandular elements is shown by the implication of blood-vessels not in immediate proximity with these structures.

Duckworth made a microscopic investigation of an iodic pustule and found that the superficial layer of the cutis vera was principally implicated. The papillary layer at the affected parts was flattened out, stretched, and even excavated, and contained a large number of small cells and a quantity of newly formed fibrous tissue. The blood-vessels were numerous and enveloped in sheaths of exudative corpsucles; no evidence of the rupture of any blood-vessel was to be obtained. The sweat glands seemed entirely unaffected, even in close proximity to the pustules. There was no implication of the hair follicles. He infers from this that the lesions are not of the nature of acne, but are due to a superficial localized dermatitis resulting in cicatricial tissue.

Farquharson attributes a marked influence in the production of iodic eruption to defective elimination of the drug, thus allowing it to remain longer in contact with the tissues of the body. This view gains support from the fact that the severer forms of the eruptions have sometimes been found associated with grave cardiac and renal disorder and the presence of albumin in the urine. The irritative effects of the iodide of potassium on the skin are, it is

alleged, often corrected by the simple expedient of giving larger doses, which stimulate the kidneys, causing enuresis and a more rapid elimination of the drug from the system. Whether the potassium combined with the iodide contributes to promote the functional activity of the kidneys has not been definitely determined. Incidentally, it may be stated that patients treated at the Hot Springs of Arkansas often take large doses of iodide of potassium, as much as one ounce per diem, without liability to incidental bad effects. The copious use of the waters, both internally and in the form of baths, no doubt produces a hyperactivity of the sudoriparous glands, as well as the kidneys, and the consequent rapid elimination of the drug.

It is worthy of note, however, that the retarded elimination of the drug does not explain the occasional occurrence of eruptive accidents within a few hours (four or five) after the ingestion of a single insignificant dose. This fact also contravenes the fanciful theory that iodic eruptions are in all cases the outward expression of evidence of a saturation of the system with iodide of potassium—an opinion formerly held by a majority of authors.

Diagnosis.—Certain forms of the iodic eruption may be confounded with variola and syphilis. The shot-like papules which precede the development of bullæ were said by Hutchinson to resemble those of the early stage of variola, but as they run their course rapidly the diagnosis is soon easily made. The occasional appearance of umbilication, caused by the vesicle spreading at its margin and sinking in the centre, is an element of confusion. The exudation is sometimes so free that crusts form not unlike those of syphilitic rupia. Other forms have been mistaken for syphilis, and iodide of potassium may be continued, possibly in increasing doses, for the very condition which it

has caused. Fox says, "I have often been consulted for supposed syphilis when the disease has been simply an iodide rash."

Tests for Iodine and Iodides.

When the quantity in the urine is small, and other tests produce doubtful results, it is necessary to eliminate organic matter by the method detailed under bromine, in which the disulphide of carbon will acquire a fine violet color if iodine was present.

If notable quantities of iodine are contained in the urine, it is often possible to detect it by one of the following methods:

1. To detect iodine in the urine, the compound is first to be decomposed by fuming nitric acid and dilute sulphuric acid, then a little starch paste, and a few drops of bisulphide of carbon are to be added, whereupon a beautiful blue color appears. On shaking it, a small portion of the iodine is dissolved by the bisulphide of carbon, and a dark-blue ring of iodide of starch is formed on the layer of bisulphide of carbon.

2. A less reliable method is as follows: After starch paste and dilute nitric acid have been added to the urine, a few drops of fuming nitric acid are added, when a blue color appears, which on heating disappears and returns again on cooling.

3. After sulphuric acid and fuming nitric acid are added, the fluid is shaken with chloroform. Then occurs, through solution of iodine in the chloroform, a violet color.

4. Sometimes the iodine is in such combination that the above agents do not free it, and it may be necessary to add chlorine water for this purpose, or the urine may have to be incinerated and then tested.

Treatment.—The treatment consists in the suspension of

the drug until the eruptive accidents have disappeared. Various expedients have been suggested with a view of preventing the occurrence of the untoward effects of the drug while continuing its use. Arsenic in the form of Fowler's solution, two to ten minims with each dose of the iodide, has been recommended, and tried in some cases with good results. Paget recommends aromatic spirits of ammonia. Aubert has recently recommended belladonna as a means of preventing the disagreeable effects of iodide of potassium. Fournier recommends that the iodide be administered with claret. According to Keyes, tolerance of the drug may often be secured by giving it in a glass of milk or large quantities of Vichy. As mentioned above, intolerance of the drug may sometimes be overcome by simply increasing the dose. It will be found that a single dose of two or three scruples in a cup of tea at bedtime is less liable to produce irritative effects upon the skin than a less quantity taken in a little water in divided doses. If evidences of the so-called "supersaturation" appear, the drug should not be again administered for four days, as that period is required for its complete elimination. Besnier claims that the drug introduced hypodermically does not give rise to the same accidents as when introduced by the stomach. A more extended clinical experience on the part of others has not verified this claim. Free use of acetate of potash and remedies of this class is to be recommended with the view of charging the system with an abundance of alkali, which may combine with any free iodine that may be present.

Ehrlich has extolled the value of sulphaniline as a prophylactic, as well as a corrective measure after symptoms of iodism have been developed. As soon as the iodism appears, a dose of four to six grams of sulphaniline is given, followed by smaller doses, often repeated if neces-

sary. The success in many of these cases, he claims, is remarkable, well-marked and even exaggerated symptoms being removed in some cases by a single dose, and after-tolerance being established. In other cases the results were not so decided. No bad results were observed from this treatment.

IODOFORM.

The cutaneous irritation which sometimes follows the external application of iodoform is doubtless due to the contained iodine. It may result from dressings of iodoform gauze or the use of the drug in powder, in ointment, or in solutions of ether, or from its absorption from the mucous surfaces of the vagina and rectum when used in the form of suppositories or injections. The eruption is usually of an erythematous character, but the inflammation may proceed to the development of vesicles and bullæ. In an examination of the literature of iodoform poisoning, Cutter found numerous references to eruptive accidents developed in connection with other toxic symptoms. They consisted ordinarily of simple erythemata or papular eruptions sometimes covering the whole body. The eruption usually disappeared rapidly upon leaving off the iodoform.

Zeissl records two cases of iodoform rash. In one case, in which an iodoform dressing was used, there appeared over the skin of the body, flexor surfaces of the arms, and the inner surface of the thighs an erythematous eruption of a diffuse bright-red color, disappearing under pressure. In the second case, the eruption was consecutive to the introduction of iodoform pencils into a sinus every second day. On the tenth day, there was itching of the extremities, followed by the appearance upon the skin of the body and extremities of an eruption of urticaria nodules

of a reddish color, from the size of a lentil to that of a three-cent piece.

Hoepfl reports a case in which an exanthem of small red spots covering the entire body was caused by an iodoform dressing to an amputated breast.

Neisser records eight cases of iodoform rash, characterized by the formation of small vesicles, and closely resembling acute eczema. In a few hours after the application, a deep redness of the surface comes on, accompanied by violent burning and itching; then vesicles filled with clear fluid appear, and soon form crusts. In some cases, the wounds dressed with iodoform took on an apparent erysipelatous action. In two of Neisser's patients, a tormenting eczema of the anus and perineum was caused by the use of iodoform suppositories. In two cases of females, similar eruptions broke out over the inner surface of the thighs whenever iodoform had been applied to the vaginal orifice.

Fabret observed an eczematous eruption in a syphilitic subject provoked by the application of an iodoform ointment.

Treves reports a case of iodoform exanthem which was somewhat peculiar in its mode of development. After iodoform had been used for three weeks to a wound of the forearm, the entire member became red, swollen, and œdematous. On the following day, a crop of vesicles, about thirty in number, appeared upon the forearm. The iodoform was discontinued, and the vesicles suppurated and healed up. Three days later, a remarkable exanthem appeared, covering the arm and shoulder and greater part of the face, the sides of the neck, and frontal aspect of the chest. The eruption consisted of patches of closely packed minute papules seated upon an erythematous base. The patches varied in size from a six-penny to that of a half a

crown piece. They were iregularly circular, with a clearly defined margin, and ran the one into the other. The eruption disappeared in two days.

The production of the iodoform rash would seem to depend upon a peculiar susceptibility of the skin to irritant influences, as in many cases the slightest trace of iodoform in any application will cause the eruption to appear.

Köster-Syke reports his personal idiosyncrasy against iodoform so marked that within a few hours after dressing a wound with an iodoform bandage, he experienced a most intense itching over the entire body attended with a slight elevation of temperature. The following night, his face, hands, and arms to the elbow, were enormously swollen and the seat of a vesicular and pemphigoid eruption. On another occasion, he used a little iodoform powder, this time taking the precaution to protect his hands with kid gloves. In ten minutes, he experienced an itching sensation in the hands and face, and in a few hours the dorsal surfaces of the hands to the tips of the fingers, the face below the eyes, and the integument behind the ears, were covered with itchy red points. A pronounced idiosyncrasy was also manifested in his case against carbolic acid.

Tests for Iodoform.

To separate iodoform from the urine, it is best to subject the latter to brisk distillation, taking care to use a cold condenser. The distillate is tested in the same manner as directed for chloroform (see chloral) by applying the isonitril reaction. In addition, it is necessary to recognize the iodine forming one of its constituents. This may be done by adding to the liquid a little nitrous acid (prepared by acting upon starch with nitric acid and heat, and diluting with about an equal volume of water). On subse-

quently adding some gelatinized starch, a tint varying from faintest purplish-blue to blue will be obtained.

IPECACUANHA.

The prolonged application of ipecacuanha to the skin causes irritation characterized by redness, and the formation of papules, vesicles, and pustules, which, on healing, are not followed by pitting or scarring.

According to Baudot, the papules are large, few in number, red from base to summit, without circumferential areola. The lesions have no tendency to run together. They are intensely itchy, and, from the scratching which they provoke, they frequently become covered with blood crusts analogous to those of prurigo. They disappear slowly. According to Delioux, the pustules may be umbilicated like those produced by antimony. A diagnostic feature is that the former do not ulcerate and leave scars. The internal use of ipecac may also occasion eruptive disturbances. Turner describes a case in which there was burning heat diffused over the whole surface of the body, together with a kind of erysipelatous eruption covering every portion, similar to what is seen after exposing the naked skin to a burning sun. Circular patches, with elevated, thick, and rounded edges, and of a fiery color, characterized the eruption.

NUX VOMICA. STRYCHNIA.

Dierbach, quoted by Piffard, says that strychnia internally administered will produce formication and pruritus, and a sensation as if the skin were pricked with needles, or there may be diaphoresis and a miliary eruption.

Skinner reports a case in which one twenty-fourth grain of strychnia produced a scarlatinoid exanthem.

OLEUM CADINI.

The oil of cade frequently excites inflammatory action when applied to the skin. The most common form is an erythematous and papular eruption, which may extend beyond the original point of application and involve a large extent of surface. This dermatitis may take on an erysipelatous form, through the implication of the lymphatic vessels in the inflammatory process.

A papular eruption, presenting many features in common with tar acne, is one of the forms of cade irritation. Baudot describes it as follows: the papulo-pustules are disseminated or united in groups, slightly confluent, but distinct from each other, implanted in the skin upon a large papular base terminating in an acuminate summit, and each perforated by a hair. The papulo-pustules are hard, solid, red, and surrounded by an areola of the same color. The suppuration is localized at the summits. Since this eruption is most abundant and characteristically developed on the hairy parts, Bazin has designated it as *sycosis cadique*.

Kleinhaus says that the hair follicles are projected above the skin in the form of nodules of the size of a hemp-seed. The susceptibility to the irritant action of the oil of cade varies in different individuals. Women are specially liable. Quite recently, a woman, aged forty, came under my observation with an eczema affecting the forearms, wrists, backs of the hands, and interdigital surfaces. A single application of the oil of cade (one to seven of vaseline) produced an intense burning, itching, and swelling of the fingers and backs of the hands extending to the wrists. Two days later, a number of large blebs were observed over the dorsal surface and sides of the middle and index

fingers. The backs of the hands were enormously swollen, and the skin studded with a large number of pin-head-sized vesicles. A week later, the hand was still œdematous, and the epidermis had peeled off from the middle and index fingers.

OLEUM MORRHUÆ.

The internal use of cod-liver oil may cause an eruption of a miliary or eczematous character. Duclos says that the eruptions of cod-liver oil are always vesicular, and spread over the entire body. Other observers, among whom is Farquharson, says that it causes an eruption of acne, presumably from the passage through the cutaneous glands of some of its acrid constituents.

OLEUM RICINI.

The only reference to the irritant effect of castor oil upon the skin which I have found is in Piffard's "Materia Medica and Therapeutics of the Skin." Langier is quoted to the effect that pruritus and erythema have been caused by the ingestion of the oil.

OLEUM TIGLII.

The application of croton oil to the skin causes more or less irritation, according to the duration of contact and sensibility of the skin. Ordinarily, after a few hours redness appears, and a copious crop of papules which rapidly become converted into vesicles and then into pustules. The lesions may first develop as vesicles without passing through the preliminary papular stage. The vesicles may be discrete or confluent, sometimes bullæ of irregular outline and of considerable size may form from their fusion. The contents of the vesicles, at first transparent, soon become turbid and purulent. The pustules are usually rounded

or globular, rarely flattened or umbilicated. At first they are tensely distended, but soon wrinkled from partial resorption of the contained fluid. The walls of the bullæ are easily ruptured, disclosing a superficial excoriation which becomes covered with a yellowish crust. The crusts usually fall off within a week or ten days, leaving a coppery pigmentation. When the inflammation involves the true skin, they may be followed by permanent cicatrices.

The volatile portion of the oil may occasion a dermatitis of neighboring parts, or secondary vesicular eruptions may appear, particularly upon the face and genitals, from accidental transference of the oil by the fingers or otherwise. In some cases it would seem that secondary eruptions are consecutive to absorption. Trousseau observed an eruption upon the scrotum when distant parts of the body were rubbed with croton oil.

OPIUM. MORPHIA.

The irritant effect of opium upon the skin has been recognized from the time of its introduction into the materia medica. While the older observers speak of an intense burning and itching as a frequent accompaniment of the use of this drug, it does not appear that they were familiar with its property of producing changes in the skin of an eruptive character. Dioscorides and Paulus Aegineta describe the *pruritus opii* as a tormenting and unbearable affection. Tralles, quoted by Lewin, published in 1774 the first observations relating to the eruptions produced by opium, which he regarded as due to increased sweating. Incidentally, it may be said that Trousseau connects the opium exanthem with a modification in the sudoral secretion occasioned by the drug, which alteration of secre-

tion, he says, determines an irritable condition of the skin, resulting in erythematous redness and pseudo-measly patches, sometimes in vesicular eruptions, and even in veritable papules when the action of the medicament has been prolonged. The production of the eruption, however, bears no relation to the stimulation of the sweat glands, as it may occur without any increase in this secretion.

The most common manifestation of the irritant effect of opium upon the skin is an erythematous eruption which may occur as diffuse uniform redness simulating scarlatina, or it may be macular like that of measles, consisting of small isolated spots of a bright or dusky red. They first appear upon the face and neck and flexor surfaces of the body, and are preceded by a hot, itchy sensation in the skin. Usually the eruption disappears promptly after discontinuing the medicine, and is followed by a slight desquamation.

Behrend reports a case of opium eruption which appeared after taking a few powders containing one-quarter grain. It was a pale scarlatinoid eruption, which on near inspection was found to consist of minute papules closely studded, distributed over the chest from clavicle to end of sternum, upon the inner side of the arms, flexor surfaces of forearms and wrist-joints, spreading down the thighs and inside of knees, and terminating at the ankle in a stripe of livid color. The pruritus was of so violent a character as to prevent sleep. The eruption subsided on suspension of the opium, but was promptly redeveloped on resuming its use. Desquamation of a branny character, foliacous over hands and feet, occurred several days later.

Morod ordered pills of opium to a lady patient who declined to take them, declaring that every time she took

opium it made her as red as a lobster. He prescribed instead *syrup diacode*, the next morning the patient was indeed red as a lobster, the eruption being accompanied with intense itching.

An exanthem resembling scarlatina has been observed on the face, neck, hands, arms, and legs of a lady patient after she had taken a single drop of laudanum. It has been observed that women are much more subject than men to the incidental irritating effects of opium.

MORPHIA.

Intense pruritus, with or without eruptive disturbance, may follow indifferently the ingestion or the hypodermatic introduction of this salt into the system. An exudative, erythematous eruption is the most frequent form of morphia eruption.

Apolant reports a case of a man who, after taking twelve to fifteen drops of a weak solution of morphia, equivalent to about four drops of Magendie's solution, had an eruption of red, wheal-like prominences on the hands and other portions of the body. The eyelids were swollen and the whole face œdematous. It was accompanied with intense burning and itching. Desquamation in large lamellæ occurred five days later. The patient, who had been ignorant of the kind of medicine ordered, recognized it from having before had a similar experience.

Scheby-Buch reports a case in which the smallest doses of morphine produced an urticarial eruption upon the face, chest, and arms, and sometimes over the whole body.

Steinboemer records a vesicular eruption after one-sixteenth grain of morphine. In the same patient, one-eighth grain of opium produced a similar eruption.

Comanos reports a case of eruption from the hypodermic

injection of 0.02 muriate morphia. It consisted of an intense, uniformly diffused, scarlatinoid redness over the throat, breast, back, and left leg (the right was slightly reddened). Recovery took place in four days, with desquamation of the epidermis.

The same quantity, given in pill form, produced a similar scarlatiniform eruption over the entire body, accompanied with intense itching. Desquamation continued for several days. Three weeks later, inunctions of morphia were used three times daily for relief of sciatica. On the fifth day, after thirteen inunctions, in which 0.05 morphia was used, the leg became reddened, and over places of inunction there appeared small pustules and blisters. Then there appeared three furuncles over the buttocks, the redness extended upwards on the back, and terminated in the formation of a large carbuncle, attended with high fever. Brivois observed, after the injection of 0.01 of hydrochlorate of morphia, a generalized eruption of discrete papules like those of prurigo, accompanied by intense itching. It was eight days before the papules disappeared. I myself have frequently observed an urticarial eruption after the hypodermic injection of morphia, which appeared indifferently after the use of small or large quantities.

Surroville reports a case in which multiple ulcerations were caused by the ingestion of morphia. The use of the drug in increasing doses from five to twenty-five centigrams caused dryness of the throat, loss of appetite, constipation, etc., soon followed by multiple ulcerations, both superficial and deep, with, sharp-cut edges, in the buccal cavity and pharynx. The ulcerations promptly healed after suppression of the drug. Again morphia was prescribed, and the ulcerations reappeared with more severity, accompanied by the same symptoms as before.

Hypodermic injections of morphia are frequently followed by inflammation and dermic abscesses which may give rise to indolent ulcers persisting for a long time without showing any disposition to heal. Two such cases have recently come under my observation; in one, a chlorotic young woman, the ulcerations persisted for some months and were finally healed up by strapping, with topical application of ung. iodoform, and internal use of potassio-tartrate of iron.

It has been observed that injections carried deep down into the subcutaneous tissues are not nearly so apt to be followed by phlegmonous abscesses as when the injection is discharged directly underneath the skin. It is also a matter of observation that hypodermic injections of morphia may be used for a long time without causing any local disturbance, when suddenly inflammatory reaction will appear, not only in recent punctures, but in those which were made two or three weeks previous. Daniel reports an aggravated case of tubercular ulcerations from hypodermic injections of morphia frequently repeated during a long period. The arms were a mass of sores from the wrists to the shoulders; the legs in like condition from ankles to knees. The eruption was tubercular in form, many of the tubercles in a stage of ulceration, discharging a peculiar grayish matter, mixed more or less with blood and very offensive when allowed to remain for a time without cleansing the parts. The discharge was acrid in its properties, excoriating or scalding the surrounding parts painfully, leaving a wide-spread, angry-looking surface which was especially marked on the patient's back and upper parts of the legs.

Tests for Opium and Morphine.

If morphine alone is detected in the urine, or meconic acid and morphine, it may be concluded that the alkaloid has been administered in form of some salt (sulphate, meconate, etc., as the case may be). If meconin can be detected in addition, opium may be assumed to have been administered. It is best to first prepare an acid extract of the urine by evaporating it to one-fourth, adding four times its volume of alcohol containing two per cent sulphuric acid, filtering after twenty-four hours, and then evaporating off the alcohol. The residuary liquid is filtered when cold.

If this is shaken with two successive portions of benzin (about equal volumes), boiling at about 176° F., the benzin solution evaporated, and the residue treated with a few drops of colorless, concentrated sulphuric acid, this will gradually assume a greenish tint, deepening to red in twenty-four hours, if meconin was present.

If meconin has been found, it is advisable to test at once for morphine. For this purpose, the remaining acid liquid is rendered alkaline, and then shaken immediately with an equal volume of warm, amylic alcohol, twice in succession. The alcoholic solution is evaporated, and the residue tested as follows:

A portion transferred to a watch-glass is treated with a few drops of diluted hydrochloric acid, evaporated to dryness below 120° F., the residue dissolved in a few drops of water, and then a drop of highly dilute solution of ferric chloride added (free from acid). There will be developed a fine blue color. A drop of nitric acid upon another portion of the residue will produce an orange or red color destroyed by sulphide of ammonium.

A few drops of Froehde's reagent (concentrated sul-

phuric acid containing, in each cubic centimetre, 0.01 gm. of molybdate of sodium or ammonium) brought in contact with even traces of morphine assume at once a magnificent violet color, which soon turns green, brownish-green, and yellow, becoming bluish-violet after twenty-four hours.

Treatment.—On account of the exceedingly evanescent character of the opium eruption, treatment is unnecessary. Bromide of potassium is said to prevent the irritant effects of this drug upon the skin.

PHOSPHORUS. ACIDUM PHOSPHORICUM.

The stimulating effect of phosphorus upon the cutaneous circulation, producing flushings and other evidences of peripheric capillary expansion, is well known. More decided evidences of irritative action upon the skin occasionally follow its use. A bullous eruption has been sometimes observed.

According to Farquharson and Ringer, purpura sometimes occurs as a symptom of its toxic action, and is usually developed in connection with gastro-intestinal derangement, icterus, etc. This observation has been confirmed in my own experience with the drug.

Hasse reports a case of pemphigoid eruption which occurred in a young girl who had been taking phosphoric acid. It disappeared on cessation of the use of the medicine, and reappeared on its resumption.

PIX BURGUNDICA.

The local effect of Burgundy pitch applied to the skin is that of a mild irritant.

It may cause, after prolonged use, an inflammation of the skin of a vesicular or pustular character, and which is apt to be persistent. Trousseau observed that a Burgundy pitch plaster, having caused the local development of a great number of vesicles, sometimes occasions a general eczema, at first acute, which may afterward become chronic.

Cazenave also alludes to its property of causing eczematous eruptions.

PIX LIQUIDA. TAR.

The external application of tar may cause an erythematous, papular, vesicular, or pustular eruption.

The tar acne, which so often develops in connection with the external use of tar, consists of small, hard, red nodules which persist for a long time after the application of the irritating agent has ceased, usually requiring from three to four weeks for their complete involution. According to Hebra, the hair follicles become inflamed and swollen so as to form papules of the size of hempseeds, or even as large as lentils. The eruption is readily distinguished from ordinary acne, in that a black tarry point always occupies the centre of each papule. Farquharson reports, as the result of an application of Ung. Picis Liquidæ to a patch of psoriasis, an intense inflammation of the sound skin over an area several inches in breadth. There was a grayish discoloration, indicating the formation of a slough, which accident was only averted by careful sedative treatment.

The internal use of tar, says Anderson, occasionally produces a copious red rash upon the skin, accompanied by fever, nausea, and other evidences of digestive derangement. Waldeck reports a case of an erythematous eruption, rubeoloid and urticarial in character, which followed the use of this drug in the form of Guyot's tar capsules.

PLUMBUM. PLUMBI ACETAS. PLUMBI CARBONAS.

The external application of the salts of lead in the form of solutions or ointments sometimes produces discolorations of the skin of a brownish or blackish character.

Foucaud de l'Espagne reports the case of a lady who was ordered the acetate of lead as an eye-wash; under the advice of another physician, she was at the same time using sulphur baths for rheumatism. A black discoloration of the eyelids ensued, which spread over the surface of the cheek bones, and was only removed after six days by washing the parts with infusions of herbs.

The internal administration of the salts of lead may cause an erythematous rash of the skin. Snow, quoted by Piffard, reports a case where the body became spotted with petechiæ from the internal use of the carbonate of lead.

PODOPHYLLUM PELTATUM.

Workmen employed in pulverizing podophyllum find it extremely irritating to the mucous surfaces with which it comes in contact, as well as to the skin.

Winterburn states that workers in podophyllum peltatum suffer from a cutaneous irritation, affecting more particularly the scrotum and genital parts.

According to Bentley, the topical application of an

alcoholic solution of podophyllum will produce rubefacient and vesicant effects.

POTASSII BICHROMAS.

The extensive use of bichromate of potassium as a mordant in the manufacture of woollen goods is a prolific cause of dermatitis.

The irritant action of the bichromate is shown in the production of eruptions of a papular and pustular character upon the hands, forearms, and exposed parts of the body. Deep ulcers and sloughs not infrequently occur, with ulcerations of the mucous surfaces and perforations of the septum nasi, constituting the so-called "chromic disease" of the dyers.

Richardson reports five cases of eczematous eruptions in workmen who were employed in a manufacturing business where the bichromate was used in a watery solution of five or six per cent. The first symptoms of irritation are heat, itching, and tingling felt in the ends and middle joints of the fingers, which soon become covered with irregular red patches upon which numerous minute elevations are seen clustered together. In the course of a day or two, these enlarge into bead-sized vesicles. In a short time these clustered vesicles run together, forming large blisters which rupture, causing the most acute pain and itching.

At this stage, pustules begin to form over the body, mainly down the spine, neck, sides, arms, and ankles, accompanied with marked constitutional disturbance, as headache, fever, loss of appetite, etc. The eruption in some cases presents, in addition to these cutaneous symptoms, the appearance of pityriasis rubra.

Harrington records a number of cases of bichromate of

potash poisoning, resulting from the manufacture and wearing of caps, gloves, and other articles of clothing dyed with this substance.

One case was that of a strong, healthy woman who worked in cloths used in making boys' caps. Her symptoms were intense itching of the hands, scalp, face, neck, and body. These were followed by ulcerations of the neck, breasts, hands, and thighs. The ears were much swollen, and became, as she expressed it, "running sores." The ulcerations about the nails resulted in the loss of three nails from one hand and two from the other.

Another case was that of a clergyman, sixty years of age, who wore a pair of brown woollen gloves. The dermatitis was limited to the parts covered by the gloves; it began with slight redness and irritation, "at first in the form of pimples, but afterward many of them ran together forming blisters." These resulted in large and deep ulcers, many of them requiring over a month to heal. Symptoms of poisoning were also observed in two boys from wearing suits of brown woollen cloth. In all of these cases chromium was found to be abundantly present in the offending articles of clothing.

In large doses, bichromate of potassium acts as an irritant poison, causing nausea, high temperature, sometimes suppression of urine and bloody stools. Few examples of cutaneous eruption are recorded from its internal use.

Quite recently, an eruption caused by wearing a grayish-brown flannel shirt dyed with bichromate of potassium, came under my observation. The patient presented himself with an erythematous eruption surrounding the lower portion of the neck and covering the entire surface of the trunks and the arms, and extending over the buttocks and upper portion of the thighs.

About the neck and over the shoulders, the eruption

was fiery red, and upon the erythematous base were observed a large number of minute papules. The eruption, which had appeared two or three days previously, was intensely itchy. Its exact limitation to the portions of the body covered by the undershirt naturally suggested the nature of the irritating cause. Chemical examination revealed the presence of chromium in the coloring matter with which the shirt was dyed.

The eruption disappeared within a few days under the influence of a simple protective powder of oxide of zinc, bismuth, and starch.

According to Burness and Mavor, it may produce a papular eruption, which later assumes a pustular character.

Hughes states that the most characteristic effects of this poison upon the skin are seen in papules, pustules, and ulcers; the ulcers have hard bases and overhanging edges, are deep, and generally dry.

Guntz, as is well known, claims the most remarkable beneficial results from the use of bichromate of potassium as a substitute for mercury in the treatment of syphilis.

Tests for Chrome Compounds.

The only salt of chromium which has been administered internally is the bichromate of potassium. Yet chrome alum and other compounds are not infrequently used externally.

If chromium is to be looked for in the urine, the following method may be recommended for its detection:

Treat the urine with an excess of ammonia, heat it to boiling, replace the excess of ammonia, if necessary; when cold, saturate the liquid with chloroform and set it aside for forty-eight hours. Pour off the liquid from any sediment; treat this with solution of soda, which will dissolve

any chromic oxide present, and boil with an excess of brown peroxide of lead, whereby the chromic oxide is converted into chromic acid.

Pour into a test-tube eight cubic centimetres of diluted and acidulated peroxide of hydrogen (commercial peroxide 5 volumes, water 24 volumes, hydrochloric acid 1 volume), pour upon it one-half cubic centimetre of ether, and then add a few drops of the liquid, which should contain the chromic acid. If the latter was present, the upper portion of the aqueous peroxide layer will turn blue. On reversing the tube a few times without shaking, the ether will dissolve out the peroxide of hydrogen and also assume a blue or bluish color.

POTASSII CHLORAS.

Although the internal use of the chlorate of potassium may cause irritant effects upon internal organs, especially the kidneys, it is not generally accredited with the property of producing cutaneous disturbances. The only references which I have found in medical literature relating to such incidental effects are the following:

Wegscheider reports, in connection with other toxic symptoms of the drug, the development of an eruption of red, non-elevated spots which became momentarily somewhat paler on pressure. They first appeared upon the arms and forehead, and spread, in the course of the following three days, over the entire body, becoming larger and of a copper-red color.

In Stelwagon's case, the patient, a syphilitic, was ordered tablets, each containing five grains of potassium chlorate—several to be taken daily.

Four days later, he returned with a "fiery erythematous and papular eruption over the neck and trunk, especially

well marked over the upper part of the back." The tablets were not renewed, and the eruption, which was regarded as erythema multiforme, disappeared in two days.

Six weeks later, the patient was again ordered the tablets, and after using them for three days, an eruption, the same in character as before, appeared; the trunk and neck were involved, and also several slightly raised erythematous spots were seen upon the legs. The eruption disappeared within forty-eight hours after discontinuing the use of the tablets.

Twice again, at the suggestion of S., who was desirous of testing the relation of the eruption to the drug, the patient took the tablets, and each time a similar eruption was developed.

RHUS TOXICODENDRON. RHUS VENENATA. RHUS VERNIX.

The irritating effect of rhus upon the skin depends largely upon individual susceptibility. While many persons are entirely insusceptible to its toxic action, others are so exquisitely sensitive that mere exposure to the volatile principle of the plant, without actual contact, is sufficient to cause the most violent cutaneous irritation. Curious examples of the remarkable potency of the poisonous emanations are vouched for on good authority, such as poisoning from walking through the damp grass in the vicinity of the plants, passing in the direct current of the wind blowing from them, sleeping in a chamber in which fresh ivy has been hung, exposure to the smoke of burning wood around which the ivy had clung, etc.

After exposure, there is a period of incubation varying from several hours to three or four days or longer, before the phenomena of cutaneous irritation begin to be manifest. The eruption is usually of an eczematous type. It

is characterized by redness, sensations of burning and itching, and the appearance upon the erythematous surface of innumerable vesicles. The vesicles spread rapidly from the starting point, if it be the fingers, along the dorsum of the hands, the wrists, and upwards along the arm. If the face be first affected, the inflammation rapidly involves the neck and extends down the trunk towards the genitals.

The vesicles often run together, forming blebs of considerable size; these may be ruptured by scratching or otherwise, and expose large denuded surfaces, which soon become covered with thin crusts and scales. The contents of the vesicles are less limpid and transparent than in ordinary vesicles; sometimes, but rarely, they become purulent, absorption slowly taking place, leaving a slight pigmentation. The œdema and swelling of the integument assume an erysipelatous character and occasion much disfigurement, especially when affecting the face. The rapid extension of the disease may be due to direct transfer of the irritating agent by the nails in scratching, or a systemic effect consecutive to absorption. The swelling of the glands which is so frequently observed in connection with rhus poisoning gives color to the probability of it being a phenomenon of absorption.

Lavini states that he applied two drops of the juice of rhus to the first phalanx of his index finger, leaving it on only two minutes, which produced, in about one hour, two black spots. Twenty-five days later, he experienced a great burning in the mouth and throat, with rapid swelling of the left cheek, the upper lips, and eyelids. The night following, the forearms swelled to twice their natural size, with a coriaceous skin, insupportable itching, etc.

Taylor brought before the New York Dermatological Society a patient who had had two attacks of an eruption presenting the characters of a dermatitis exfoliativa, from

handling the twigs and leaves of the rhus venenata. The eruption commenced on his wrists and spread over the entire body ; there was an abundant desquamation, and the lunulæ of the nails were affected, being wrinkled and thicker than natural. The second attack was experimentally produced six months later by rubbing the dried leaves over the left hand. Four days later, he complained of itching and burning over the left deltoid muscle, the thighs, and genital organs. The conjunctivæ soon became reddened and the entire skin was covered with large red blotches, which soon became diffuse, resembling a scarlatinal exanthem. The exfoliation was much slighter than in the first attack.

White observed in a pregnant female an eruption of papules and pustules upon the abdomen, arms, and dorsal surfaces of the hands from ivy poisoning. One of the pustules on the left arm attained the proportions of a well-developed boil. Confinement took place about the time the disease was disappearing. On the sixth or seventh day after birth, there was observed on the child's belly an eruption identical with that from which the mother suffered. White regards this as an instance of the communication of a maternal affection to the child in utero.

Hubbard observed in a patient a vesicular eruption covering the whole body, attended with severe burning and itching, from eating a root of rhus which he had mistaken for sarsaparilla. The eruption differed from that produced by external contact only in the size of the vesicles which were smaller.

The same character of cutaneous disturbance may follow the internal use of rhus in medicinal doses. Piffard reports a case of a female patient for whom he had ordered two-drop doses of the tincture of rhus, to be taken morning and evening. On the third day, he was called to treat the

patient for erysipelas of the face, which presented all the characteristics of a rhus eruption.

Other observers speak of erysipelatous inflammations, pustules, boils, etc., resulting from the ingestion of rhus in small doses.

The rhus vernix which grows in Japan seems to be endowed with more marked irritating properties than either of the other varieties. A number of cases of erythematous and vesicular eruptions have been observed from the handling of Chinese lacquer work, in the varnishing of which this variety of rhus is used.

In a personal communication from Dr. H. S. Allen, of Seoul, Korea, he states that natives, as well as foreigners, are often attacked with what is termed in that country "varnish poisoning." It comes on after contact with furniture or other articles recently varnished. Some persons cannot pass a furniture shop where articles are being varnished without being poisoned. His personal experience is thus related: "My first eruption occurred in Nanking. The dermatitis first developed over my left eye, spreading to my forehead and nose; it itched and burned, causing great discomfort and inconvenience. Being ignorant of the effect of the Chinese varnish, I diagnosed the trouble as herpes zoster frontalis. The next attack was in Shanghai, after receiving a new chair from a Chinese cabinet-maker. The skin of the forehead became hot and itched intolerably, and was soon covered by an eruption of minute vesicles on a raised base. The swelling increased until the eyes were nearly closed. It was first diagnosed as a facial erysipelas, but consultation being called, it was pronounced 'varnish poisoning.'"

Treatment.—The inflammatory changes in the skin met with in rhus poisoning are essentially the same as those determined by other irritating agencies, and the general

principles of treatment indicated in rhus dermatitis will be found applicable to other drug eruptions of an eczematous type. The various therapeutic measures which have been recommended may therefore be considered somewhat in detail. Is it well to remember that in all these cases the inflammation is self-limited, with a tendency to spontaneous recovery; the principles of rational treatment are to relieve the subjective sensations of burning and itching, and to modify the inflammatory action.

With a view of circumscribing the spread of the eruption, the patient should be cautioned against bringing the hands in contact with other parts of the body; especially should he be enjoined against handling the genital parts, as the integument of this region is peculiarly susceptible to the irritant action of the rhus. It is a matter of common observation that the genital parts of the male are much more frequently the seat of the eruption than the corresponding region in the female, and the explanation is found in the direct transfer of the irritating agent by the fingers in handling the parts during the act of micturition, in dressing, etc.

The treatment of the acute stage of the eruption should be essentially soothing and protective. For this purpose, dusting powders and sedative or mildly astringent lotions should be used.

The following lotion may be employed: ℞ Sodii hyposulphitis, ʒ i.; Gylcerinæ, ʒ ss.; Aq., ad ʒ viij. M. Apply with compresses dipped in the solution and frequently renewed. A strong solution of the sulphite of sodium may be used with benefit. In cases where the continuous application of a lotion is impracticable, freely dusting the surface with an absorbont powder is to be recommended. Pear's Fuller's Earth, which is perfectly bland and unirritating, may be employed, or the following combination:

℞ Pulv. Zinci oxidi, ʒ ij.; Pulv. bismuthi subnitratis, ʒ i.; Pulv. amyli, ʒ v. M.

It is important that the affected surface should be kept copiously covered with the powder; an occasional sprinkling does little good. If there is much burning heat present, a little powdered camphor (ʒ ss. to the ℥ i.) may be added.

When the more acute eruptive features have begun to subside, a mild, soothing ointment should be employed. For this purpose, nothing is better or more universally applicable than the ordinary benzoated zinc ointment. Another very excellent dressing in this stage of the disease is the Lassar paste: ℞ Pulv. zinci ox.; Pulv. amyli, āā ʒ ij.; Vaselini, ʒ iv. M.

The good effects of the same treatment will be found to vary in different patients. There is a great difference in the susceptibility of different individuals to irritant action, and the difference in susceptibility is perhaps equally marked in relation to the influence of medication.

It is not possible to here enumerate the entire list of remedies which have been recommended in the treatment of rhus-poisoning, for their name is legion. To give only a few which are claimed to possess a remarkable efficacy in subduing the symptoms: lime-water; carron oil; alum curd; a saturated solution of bicarbonate of sodium; a strong solution of chlorate of potassium; a solution of sulphate of zinc (℥ ss. to the pint); a solution of carbolic acid (grs. ij.–iv. to the ℥ i.); a weak solution of sulphate of copper; dilute lead-water, etc. Compresses to be wet with these lotions, and applied every hour or two through the day. Dr. White, of Boston, and others highly praise the efficacy of the ordinary black wash. Dr. Brown, U. S. N., claims that bromine (ten to twenty drops to the ounce of olive-oil or cosmoline) is a specific.

To turn now to the vegetable materia medica: a decoction of white-oak bark; a decoction of the bark or leaves of the elder; an infusion of the sweet fern; the tincture or fluid extract of serpentaria, lobelia, sanguinaria; infusion of the bark of the red sassafras, with sassafras tea, *ad libitum*, internally, have all been highly spoken of. Probably the most efficient of the vegetable remedies is the grindelia robusta, which may be used in the form of the fluid extract, diluted in ten to thirty parts of water.

Dr. Hyde speaks enthusiastically of an ointment made by incorporatiug a decoction of the inner bark of the American spicebush (Benzoin odoriferus) with cold cream. Belladonna, the green vegetable bruised and mixed with cream, or in the form of the officinal ointment, has also been recommended. Dr. Edson highly extols the virtues of gelsemium in the treatment of rhus-poisoning. His formula is: ℞ Acidi carbolici, ʒ ss.; Fl. ext. Gelsemii, ʒ ij.; Glycerini, ℥ ss.; Aq., ad ℥ iv. M. Cloths to be moistened with this lotion, and applied to the affected parts. This, he claims, with the internal administration of the fluid extract of gelsemium every three hours, effectually relieves the burning and itching, and the eruption speedily disappears.

Dr. White, of New York, recommends the following formula; ℞ Acidi carbolici, ♏ xx.; Glycerite of cocaine (four per cent), ʒ ij.; Vaseline, ℥ i. M.; or ℞ Acidi carbolici, ʒ ss.; Glycerite of cocoaine (four per cent), ʒ iv.; Aq. laurocerasi, ℥ i.; Aq. Rosæ, ℥ ij. M. Either ointment or lotion to be applied several times daily. The plan of treatment found most serviceable in China for rhus dermatitis is, according to Dr. Allen, the constant bathing of the affected surfaces with an infusion made from freshly cut shavings of camphor wood. The offici-

nal preparations of camphor were not found so serviceable.

SANTONINUM. SODII SANTONAS.

Sieveking reports the occurrence of an eruption in a child after taking three grains of santonine. A wheal first appeared on the nose, and later there appeared an urticarial eruption over the entire surface of the body. A second dose of three grains promptly reproduced a general urticaria attended with so much œdema as to render the child unrecognizable. After a warm bath, the eruption disappeared in the course of an hour or two.

Hubert observed in a number of patients who had been taking from ten to twenty centigrams of santonate of soda an eruption characterized by a large number of pin-head-sized vesicles situated upon the trunk and limbs, but sparing the face. The vesicles never became confluent; they gradually shrivelled and disappeared, giving place to a slight epidermic exfoliation.

SINAPIS.

The external application of mustard causes sensation of itching, burning, and violent smarting, and, if the application be long continued, vesication, and even ulceration may result. According to Dierbach, pustules and violent erysipelatous inflammation may follow. Rayer observed, towards the close of the cholera epidemic in 1832, in a large number of patients, erythematous inflammations which lasted several weeks, produced by cataplasms of *Farine de moutarde.*

STRAMONIUM.

The demonstrated identity of daturia with atropia, the active principle of belladonna, would lead us to infer a similarity of action upon the skin. In the property of producing cutaneous disturbances, stramonium seems to occupy a position intermediate between belladonna and hyoscyamus, the two drugs with which it has such close botanical affinities.

The most common form of eruptive disturbance from the internal administration of stramonium is erythematous. The eruption is scarlatinoid in character, the redness bright and vivid, and attended with a sense of burning and itching.

Roth reports a case of stramonium poisoning, in which the face and body were swollen, as if dropsical, and covered with a scarlatiniform rash.

Liegey records a case of generalized scarlatiniform eruption, with pronounced angina, from the use of this drug.

Meigs observed from the use of stramonium hundreds of small brilliant petechiæ on the face, neck, and breast of a patient, many of which had a stellate form. An erysipelatoid inflammation has also been observed to follow the use of this drug.

SULPHUR.

Sulphur exerts a stimulating influence on the skin. Strong applications cause irritation, characterized by redness, papules, confluent and painful vesicles. An artificial eczema is a common result of the application of strong sulphur ointment. The simple contact of the vapor in fumigations may produce a similar effect. Rayer says that he has often seen persons attacked with vesicular or papular eruptions after the employment of sulphur vapor baths.

According to Bazin, the sulphuret of potassium or sodium dissolved in water determines an intense irritation of the skin, which may be extreme, if the strength of the sulphur be considerable, or the temperature of the bath elevated. He observed as a result of four or five frictions over the lumbar region of four grams of sulphuret of potassium to thirty grams of water, a violent inflammation, characterized by pustules, dermic abscesses, and veritable phlegmons.

Baudot states that, under the influence of sulphur lotions and ointments, there results an irritation which is manifested by an active fluxion, quickly followed by a crop of very minute confluent vesicles, which are distended with a purulent or sero-purulent fluid, and surrounded by an inflammatory areola, two or three times the diameter of the vesicles; this eruption is quite painful.

According to Trousseau, the critical fluxion to the skin, known in technical language as *la poussée*, is a familiar phenomenon in patients who use thermal sulphur baths. It is manifested by small papules, and often a painful, confluent vesicular eruption.

The internal use of sulphur in medicinal doses often

produces a dark coloration and much irritation of the skin, with eruptions of an eczematous character. Phillips has observed a red, papular eruption from the internal use of sulphur, and also, occasionally, boils and carbuncles. The waters of Harrogate, Bareges, Aix la Chapelle, etc., have been known to produce such effects.

De Schweinitz reports a case of scarlatinal rash which covered almost the entire surface of the body, especially well marked upon the face, chest, and neck, supposed to be due to the free use of flowers of sulphur in a gargle. It was observed that the exanthem grew worse after each employment of the gargle.

TANACETUM. TANSY.

The only instance of eruptive disturbance from the internal use of tansy found on record is an observation of Porter. He observed a varioliform eruption in a young woman produced by the ingestion of one and a half ounces of oil of tansy, taken for the purpose of abortion.

THAPSIA.

The application of this resin to the skin in the form of a plaster produces a rubefaction, accompanied by a very intense miliary eruption, analogous to that caused by croton oil. Trousseau states that the eruption produced by thapsia differs from that produced by croton oil in the following points: 1, in its uniformity and regularity, all the pustules being alike; 2, in the large number of pustules, and, 3, in the rapidity with which pus appears in the vesicles.

According to Tournadre, the redness and swelling produced by Thapsia may be mistaken for erysipelas.

I have seen a pustular eruption on the face from the

application of a thapsia plaster on the chest for the relief of bronchial irritation.

TURPENTINE. OL. TEREBINTHINÆ.

The external application of turpentine causes irritation, manifested by sensations of burning and smarting, redness, vesicles, blisters, and other inflammatory changes. The vapors of turpentine may also produce a burning, itching, erythematous eruption. The dermatitis caused by oil of urpentine is often of an obstinate character, and may persist long after the cause which occasioned it has been withdrawn. It proves very intractable to treatment.

The internal use of turpentine in medicinal doses may also cause eruptive disturbances of different degrees of severity. The most common form is an intense erythema of vinous red hue, invading by preference the face and upper portion of the trunk. It may be accompanied by a profuse eruption of minute papules which often develop into vesicles, and then into pustules presenting a distinctly eczematous type. Brochin reports a number of cases in which an erythematous or urticarial eruption was observed after the ingestion of turpentine.

Berenguier reports a case in which large doses of the drug produced a scarlatina-like eruption, spreading over the face and upper part of the body in irregular patches—numerous minute acuminate papules covered the surfaces. The next day, the oil having been continued, the eruption spread to the lower limbs.

As in the case of dermatitis from the external application of turpentine, the eruptions from its internal use manifest the character of persistency. Even after the eruption has disappeared, and desquamation has taken place, the subjective symptoms of itching and irritation may continue for an indefinite period.

Terebene, one of the derivatives of turpentine, likewise possesses the property of producing cutaneous irritation. Garland reports the case of a patient, aged sixty years, who took five-minim doses four times a day for chronic bronchitis. After taking six doses, he had to desist on account of a profuse bright-red papular rash, intensely itching, making its appearance first on the left hand, then on the ankles, extending up the legs to the knees. The patient had previously displayed an idiosyncrasy against turpentine. A turpentine liniment applied to a sprained wrist caused a rash identical with that above-described, and a swollen condition of the other arm.

The presence of oil of turpentine, or of terpenes or camphenes in general, is chiefly recognized by the peculiar odor of the urine. It is often possible to distinguish the source in this manner.

VERATRIA AND VERATRUM VIRIDE.

Although veratria is commercially derived from another source than veratrum viride, it will be convenient to consider together their irritant action upon the skin.

Veratria, which is rarely used internally, causes, when applied to the skin in the strength of the ordinary ointment, sensations of tingling, smarting, and increased heat, not only at the point of contact, but on remote parts of the body. When applied in a concentrated form, it is highly irritant, producing erythema, and even pustular and petechial eruptions.

Veratrum viride is also irritant to the skin, its local application causing redness and burning.

The internal use of veratrum viride sometimes occasions an erythematous condition of the skin attended with sensations of pain. Forcke, quoted by Lewin, observed a

pustular eruption on the face, most marked around the mouth.

The use of the drug hypodermatically is sometimes followed by painful swellings around the point of puncture, with extensive erythema. Eulenburg witnessed the formation of an abscess in one case.

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