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The therapeutical history of iodine does not extend over a very long period of years. The element was only discovered in 1812, and was first introduced into medicine in 1820 by Coindet of Geneva, when, in a short paper entitled *Découverte d'un nouveau remède contre le goître*,[1] he drew general attention to the efficacy of iodine and the iodides of potassium and sodium in causing the disappearance of soft bronchoceles. But the use of iodine in goitre, although in much less convenient form, dates back to a very remote period. The ash of bladder-wrack (*Fucus vesiculosus*), and burnt sponge, were well-known remedies at the time, and, in searching for the active constituent common to both, Coindet came to the conclusion that it must be iodine, a conjecture which his therapeutical observations very soon showed to be correct. The knowledge of the value of burnt sponge in goitre and scrofula had been widely spread by Arnaud de Villeneuve (thirteenth century), but it had long previously been in less general use in Europe, while in China and among the natives of South America marine algae and certain iodine waters seem to have been employed in similar cases from prehistoric times.

Coindet's discovery gave a great impetus to the use of iodine and its compounds in medicine; but notwithstanding the many researches which have since been made into their exact mode of action, this still remains obscure in many important particulars, most writers escaping the difficulties by

classing them vaguely as "alteratives." The ordinary methods of pharmacological investigation, such as the examination of the circulation, the nervous system, blood, etc. in animals under the influence of iodides, have conspicuously failed to explain satisfactorily many of the reasons of their undoubted therapeutical activity. On the other hand, the knowledge which we have now obtained of the functions of the thyroid gland, of the absolute necessity of its secretion for healthy existence, and the fact that Baumann and Roos[2] have proved that an iodine-containing organic compound is the active constituent of the secretion, afford a probable explanation of certain of the actions of iodine in diseased conditions, and of some at least of its occasional deleterious effects.

We may begin with goitre in which iodine is the remedy *par excellence*. Coindet and others soon found that while most cases of goitre rapidly improved under iodine, yet a few of them developed very alarming symptoms, and some deaths were recorded. Nearly all contemporary writers attributed these results to the direct poisonous action of the iodine, and the remedy came to be regarded with much distrust. The symptoms varied only in degree, and consisted in great and often alarming emaciation, atrophy of the breasts or testicles, rapid heart-action, palpitation, tremors, nervousness and sleeplessness. These cases were not uncommon in Switzerland, and occurred with such small doses as $\frac{1}{100}$ to $\frac{1}{30}$ grain iodine, or $\frac{1}{24}$ grain potassium iodide daily. It is quite clear now that these symptoms are due to thyroid poisoning, an increased secretion, or increased discharge of the secretion into the blood, being evidently provoked by the administration of iodine. I have lately seen exactly similar symptoms occur in a lady, aged 36, during the cure of a goitre for which no iodine was given. She had a large soft goitre which was causing absolutely no symptoms except a little discomfort in swallowing. On her going to the country for change of air, the goitre began to diminish rapidly in size, and she suffered from emaciation, nervous excitement, tremors, excessive palpitation, and insomnia. The goitre completely disappeared in about two months, the symptoms persisting for three months

longer, after which she gradually recovered. Here, iodine played no part whatever in producing the symptoms. Prévost, Lebert,[3] and Röser[4] in discussing these cases had, at different times, expressed the opinion that the condition might be due to poisonous products from the breaking-down goitre; but as nothing was then known regarding the function of the thyroid, no attention was paid to their views, the iodine was universally regarded as the cause, and the condition received the name of "iodism" or "iodic cachexia." It has been often seen in goitrous dogs to which iodine has been given, and many cases have been recorded by Rilliet,[5] in some of which burnt sponge, or small doses of iodine-containing mineral waters, and even living at the seaside, have induced it in goitrous men or women.

It is a difficult matter to decide whether these symptoms ever occur in non-goitrous persons on the administration of iodine. Even the existence of this form of "iodism" has been denied. Ricord and Velpeau in Paris, out of 15,000 cases[6] in which iodine or potassium iodide had been given, never saw an instance of it, and Hermann[7] in Vienna, with 50,000 cases, was in a similar position. It is certainly therefore very rare, but, in a few cases, loss of subcutaneous fat and atrophy of the mammae or testicles have apparently followed directly on the use of iodine and iodides. Most writers of text-books seem to regard atrophy of glands as a common effect of iodides, but this is not my opinion, and on consulting the original records of reported cases I find it usually stated that the persons who suffered in this way were goitrous. This most important element in the case has generally been omitted in the citation or abstract. But it seems quite clear that, when these effects do occur, they are not primarily due to iodine or iodides, but to an increased secretion of thyroid juice provoked by the drug. A more careful examination of these cases might have revealed an enlarged thyroid gland.

Owing to the rarity of this form of "iodism" in all countries in which goitre is not endemic, it is very little known, and hence the more familiar form of poisoning has gradually come to be labelled "iodism." The symptoms of it are very familiar, and

arise from irritation of the nasal, buccal, and respiratory mucous membranes, accompanied by skin eruptions, and a very considerable feeling of depression. Common as it is, we have no exact knowledge of the conditions under which it occurs. It is generally assumed that the irritation is due to free iodine, but the element has never been detected "free" in any case. It sometimes develops on one side only of the nasal mucous membrane, and hence the conditions which induce it must be local. It has been suggested that the iodides are decomposed by ozone,[8] by carbonic acid,[9] by nitrites,[10] and by the lymph cells,[11] but none of the theories advanced stand the test of experimental criticism. Numerous methods of preventing its occurrence have been suggested. Ehrlich and Kroenig[12] advise large doses of sulphanilic acid upon the theory that it will combine with the nitrites present and prevent them decomposing the iodides. It is doubtful if this union could take place *in corpore*, and the suggestion resolves itself into a theoretical remedy to counteract a still more theoretical cause of the condition. Quinine,[13] bromides,[14] potassium bicarbonate,[15] and sarsaparilla[16] have all been advanced as preventives, while arsenic and strict cleanliness have been said to lessen the tendency to skin eruptions. I may say that I have frequently tried all these so-called preventives of iodism except sulphanilic acid, but have never seen any benefit from them. A statement is frequently made that by doubling or increasing the dose of iodide the coryza and other symptoms may be cut short. My own experience is very distinctly contrary to this, as I find that either stopping the medicine or lessening the dose usually causes a rapid abatement of the symptoms, while an increase of dose tends to aggravate them. On searching through the literature of the subject, I have been unable to find any authority for the statement that an increase of the dose cuts short the attack.

In aneurism the value of potassium iodide is now well established. The explanation given of its beneficial action has usually had reference to a supposed depressing effect on the heart, with dilatation of the small arteries, and lowering of blood pressure. But experiments have shown that no such

actions can be rightly attributed to it. Iodine and sodium iodide have only a very trifling action on the heart and circulation, while potassium iodide owes its effects in this direction to its potassium component, and as long as it is given in only moderately large doses it tends to strengthen the heart's beat and raise the blood pressure, rather than to depress them.

In atheroma, also, iodides have in many cases, even in those which are not syphilitic, a retardative and sometimes, apparently, a curative effect, no explanation of which has been forthcoming. It is probable, however, that in some of these cases early atheroma and aneurism may be due to a lessening of the thyroid secretion, and that the iodide has a counteracting effect on this. Vermehren has pointed out that premature senility and myxoedema have many features in common. The change in the expression, the falling out of hair and teeth, the dryness of skin, the dulling of the nervous system, the decreased metabolism, the low temperature, and sensitiveness to cold, all strike one as features common to both. The changes in the arteries and capillaries (increase of connective tissue and its consequences) are also common to both conditions. There must be many factors in the changes consequent on old age, but it is highly probable at least that a degree of failure of the thyroid secretion is one of them. This seems also to have occurred to Horsley, who remarks that in his opinion an active thyroid gland is a necessity for maintaining a vigorous old age. If this be so, the increased secretion of thyroid juice under the action of iodides may lead to an absorption of the atheromatous tissue, such as occurs in myxoedema, but of course on a much lesser scale.

In tertiary syphilis, also, it seems highly probable that absorption of new growths is not so much due to a primary iodine action as to some stimulating effect of the drug on thyroid activity. The prevailing theory of the action of potassium iodide in syphilis is that the salt is broken up by some unknown agency in the new growths, that the free iodine combines with and breaks down the albumin

of the cells, which then die and become absorbed. Hence the prevailing idea that the larger the dose the better the action. Such a chemical reaction as has just been described is, to say the least, most improbable, and there are, besides, certain facts which militate against this view. Coindet, Mayo, and others cured syphilis with very small doses of iodine, and iodide of potassium was at first given in $\frac{1}{2}$ to 2 grain doses. Iodoform, iodothyrin, and ferrous iodide have been successfully used in syphilis in very small dose, although not so effectively perhaps as larger doses of the alkaline iodides. Potassium bromide is absolutely ineffective in syphilis, and therefore the cure of tertiary growths is an iodine action, and is quite marked with any dose. The most probable explanation is that the iodine acts in these cases by bringing about an increased secretion of the powerfully resolvent thyroid juice, and we know that small doses are capable of doing this under certain diseased conditions. Healthy persons can take very large quantities of potassium iodide[17] (up to 600 grains per day or even more) without suffering any ill effects, except perhaps thirst and some slight catarrh, hence it seems probable that the salt passes out of the body without any of its iodine being utilized by the thyroid or other cells. In short, it has in health no more action than a similar amount of sodium chloride would have, that is to say, only a purely saline action. In disease it is probably utilized by the thyroid gland, and hence its different effects. We have an analogous state of affairs in the case of iron. In health, when the haemoglobin and corpuscles are normal, the administration of iron does not increase either, nor has it any apparent action on them, but as soon as anaemia occurs the utilization of the iron is immediate and its effects most marked.

In lead and mercurial poisoning it is probable that alkaline iodides act simply as salts, and have not any specific iodine or thyroid action. The discovery of their efficacy in these cases is due to Melsens.[18] In hardening tissues with mercuric chloride for microscopic examination,

he removed the metal with potassium iodide, and on his recommendation it was successfully used in mercury poisoning in man. Shortly after, it was also very successfully tried in lead poisoning. Bromide of potassium is stated to be quite as effective in these cases, but I myself have no experience of it. Both of them most probably owe their efficacy simply to their chemical properties of being able to dissolve up albuminous compounds of lead and mercury, which then become capable of excretion by the kidney.

Such considerations are to a certain extent theoretical, and must remain so until more systematic clinical investigation has been made into the action of iodides; but few drugs are used in more haphazard fashion, and until we obtain more precise information regarding their mode of action and the conditions under which they act, it is hopeless to expect any advance in precision in their practical clinical application.

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