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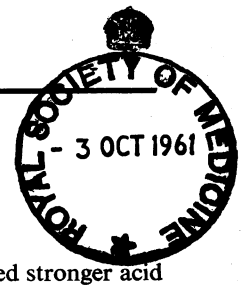


Meeting June 14 1961

President's Address

Iodine in Medicine and Pharmacy Since its Discovery—1811-1961

by Francis C Kelly BSc PhD FRIC (*London*)

To compress into one brief hour the whole medical history of iodine since its discovery by the French chemist, Bernard Courtois, one hundred and fifty years ago, is manifestly impossible. I propose, therefore, to follow only one or two of the more important threads that make-up the warp and woof of what for me has always been a fascinating story.

Like so many other scientific advances, the discovery of iodine was a discovery quickened under the urgency and pressure of war. At the beginning of the nineteenth century, France, obedient to the dictates of Napoleon's ambitious dreams, was fighting with almost all her neighbours and she needed enormous quantities of gunpowder to do the job. Hemmed-in on land by the armies of Prussia and Austria, and blockaded at sea by the British Navy, her supplies of chemicals necessary for the manufacture of gunpowder were cut off. One of these chemical essentials was saltpetre – nitrate. What did France do? As she was unable to get nitrate from beyond her borders, she made it at home, artificially, in specially constructed nitre beds. And it was while engaged in the manufacture of saltpetre on one of these artificial 'nitre plantations', near Paris, that Bernard Courtois made his discovery.

The story has often been told. The key-point is that to make saltpetre you must have a plentiful supply of soda. Courtois obtained his soda from the ashes of seaweed – called variously *varec*, *varech*, or *vareck* in French, and *wrack* or, more commonly, *kelp* in English. Extraction of the soluble sodium carbonate from the seaweed ash was carried out in metal vats, and after successive extractions there remained at the bottom of the vessels a thick mother liquor encrusted with insoluble material.

From time to time it was necessary to clean out these deposits with the aid of acid and heat. It seems that one day Courtois added stronger acid than usual, for he was astonished to see intensely beautiful violet-coloured vapours arising from the mixture. He noticed, furthermore, that these vapours formed a deposit of lustrous metal-like crystals on the cooler parts of the vessel.

Here was a new and strange phenomenon. His curiosity aroused, Courtois scraped off some of the mysterious substance, and, by a brief examination, determined its more obvious chemical properties. But he was far too busy with the management of his saltpetre factory to carry his investigations very far; so he gave specimens of the new product to his closest professional friends asking them to continue the study where he had left off. Among those who received specimens were Gay-Lussac, the most distinguished French chemist of his day, and also Ampère.

Now, all this happened towards the end of the year 1811 – probably in the month of November – the exact date of the discovery of iodine is not known.

Two years elapsed.

On October 27, 1813, there arrived in Paris from England a remarkable quartette. They were: Sir Humphry Davy, the eminent English chemist; his temperamentally unpredictable wife, Lady Davy; her lady's maid; and Davy's assistant and valet, none other than Michael Faraday, then an obscure young man of 22, who was eventually to become more famous than his master.

Remember that England was then at war with France; but in those days wars were solely the affair of soldiers and sailors; men of science continued to correspond with each other and remained constantly on good terms. So it was that when Davy expressed a desire to pass through France on a journey to Italy, Napoleon, always an ardent patron of science, immediately ordered that passports be issued.

Among the first to greet Davy on his arrival in Paris was Ampère who, in an eager and generous moment, gave Davy a sample of the unknown 'X', as they called it. Davy got to work upon it and soon satisfied himself that it was a new elementary

substance analogous to chlorine. On tour, Davy always carried a compact travelling laboratory around with him – a 'chemistry set' we would call it nowadays.

Gay-Lussac – Davy's only professional equal in France, or indeed anywhere else – was furious when he heard what Ampère had done. His irritation is understandable. He was annoyed, not so much with Ampère, as with himself for being so slow. After all, he had had substance 'X' in his hands for two years and had already proved its elementary nature; but alas, had published nothing.

There followed an undignified scramble into print to establish priority, and a bitter 'priority' quarrel broke out between Davy and Gay-Lussac. The details need not detain us; they are well documented.

For posterity, the happy outcome of these controversial days was the birth of a new and beautiful element. Its name, given by Gay-Lussac in French – 'iode' – and anglicized by Davy – 'iodine' – is derived, like so many of the loveliest words in English, from the Greek – from the word ἰοειδής meaning 'violet coloured'.

From Folk Medicine to Rational Therapy

Comparatively soon after its discovery, iodine found favour as a therapeutic agent – a medicine.

Looking backwards from the precarious heights of 1961 down through the past century and a half, we can discern two distinct lines of advance which could not, of course, be foreseen by those who launched iodine upon its medical and pharmaceutical career.

The first illustrates perfectly how, as medical science progresses, the unexplained virtues of a traditional remedy – some part of folk medicine, let us say – become wholly intelligible when exposed to the light of exact biological knowledge.

In 1656, more than one hundred and fifty years before the discovery of iodine, a London physician called Thomas Wharton described and named a gland in the neck: he called it the *thyroid* gland – the shield-shaped gland. He says: 'It contributes much to the beauty of the neck, filling-up the vacant spaces around the larynx, making its protuberant parts smooth, particularly in females, to whom for this reason a larger gland has been assigned, which renders their necks more even, and more beautiful.' Unhappily, thyroid glands do not always retain these delicate proportions. They sometimes get out of gear inside, and grow into the large unsightly swellings that we describe under the general term of goitre.

Goitre has troubled mankind from time immemorial; and from time immemorial man has sought to overcome it. Centuries before the discovery of iodine, the most highly-prized remedy for goitre was a concoction containing the ashes of burnt sea sponge. Some say that this remedy originated in the very early medical experience of China, where goitre then abounded and indeed still abounds. Certainly the burnt-sponge remedy was known to European medicine in the Middle Ages (thirteenth century, let us say) and eventually found its way to England, where, in the mid-1700s, burnt sponge was famed as the 'Coventry Remedy'.

For many a year, the Coventry recipe was held secret by the family of a Dr Bate of that town. They administered it with such success as to gain them a wide reputation and no small fortune. Only in 1779 was it disclosed that the essential ingredient was burnt sponge.

Now, in 1819, eight years after the discovery of iodine, Andrew Fyfe, then lecturer in chemistry at the University of Edinburgh, found that the common sea sponge always contains exceptionally high quantities of iodine. Although Fyfe did not realize it, his discovery was important because it provided a link in the chain of evidence that proved iodine to be the active curative principle in burnt sponge.

In the same year (1819) a prominent physician in Geneva, Jean François Coindet, ignorant of Fyfe's findings, but aware of the virtues of burnt sponge and of seaweed ash as remedies for goitre, suspected that iodine, discovered in seaweed but a few years earlier, might be the active therapeutic agent common to these two marine products.

Coindet's test of this hypothesis met with dramatic success. By giving tincture of iodine to goitre patients – there were plenty of them in Switzerland, his native country – he could appreciably reduce large goitrous swellings within a week. So spectacular were his results, that everywhere they gained a wide publicity, and Coindet is generally regarded as having been the first to introduce iodine into medical practice in this way.

Claims for this honour have also been advanced by the celebrated English physician and chemist, William Prout, who stated (in 1834) that he first employed potassium iodide as a remedy for goitre in 1816. He says, also, that he told Dr John Elliotson about it, and that Elliotson commonly prescribed potassium iodide at St Thomas's Hospital as early as 1819.

Although these claims cannot be verified in any contemporary record, there is no reason to doubt them. Incidentally, Dr Elliotson was the first President of this Society after its incorporation as the Royal Medical and Chirurgical Society of London in 1834; his name appears in our first Charter, and there is a good portrait of him in the Council chamber on the 4th floor.

Hard on the heels of Coindet's remarkable therapeutic results came the suggestion that the cause of goitre is a lack of iodine in the system

brought about by a deficiency of the element in water, soil, and food. Credit for this belongs to the French chemist, Gaspard Adolphe Chatin who, between the years 1850 and 1876, found that the iodine content of waters, and of foodstuffs of vegetable origin grown in goitre areas, was less than that in healthy areas.

Unfortunately, Chatin's conclusions failed to convince his contemporaries, and his attempt to establish a causal relationship between environmental iodine deficiency and the occurrence of endemic goitre lay neglected and forgotten until the end of the nineteenth century.

To-day, the opinions of Coindet and of Chatin stand completely justified. First step in their vindication was the fundamental discovery in 1895, by the German chemist Baumann, that iodine is an invariable constituent of the normal thyroid gland. This at once gave point to the iodine treatment of goitre introduced by Coindet seventy-five years earlier. Next major advance resulted from investigations carried out between the years 1913 and 1919 by E C Kendall at the Mayo Foundation, Rochester, N.Y., who was the first to isolate the iodine-containing hormone of the thyroid gland in crystalline form. He named it 'thyroxine'. Then came the notable work of Sir Charles Harington, around the years 1925 to 1930, who determined the exact chemical constitution of thyroxine, proved that the molecule contains four atoms of iodine, devised means for its artificial synthesis, and drew attention to the principal chemical features responsible for its specific physiological activity.

'It is interesting to reflect', writes Sir Charles, 'that even if we date the first therapeutic use of burnt sponge from the middle of the thirteenth century, this remedy was known as a specific for thyroid disease some five hundred and fifty years before the discovery of the element to which it owed its activity, and some six hundred and fifty years before the final demonstration of the role of the element in the economy of the thyroid gland itself.'

This gradually unfolding knowledge brought a new outlook on the whole question of local iodine deficiency as a cause of goitre. Soils, foods, and drinking-waters from goitrous and non-goitrous regions have been examined afresh by refined modern techniques, and the results amply confirm Chatin's dictum that where iodine is scarce – either in absolute or relative terms – there also will you find goitre.

Through the enlightened efforts of the World Health Organization goitre surveys have been carried out all over the world in recent years and we now have 18 major countries where, by law, all kitchen and table salt is iodized in the interests of public health. Twenty others, hesitant to impose legal compulsion, nevertheless officially encourage the community use of iodized salt as a preventive measure in the public interest.

After all, according to best estimates, there are in the world to-day 200 million people who suffer from thyroid deficiency in greater or lesser degree.

I would mention here that iodization of salt to prevent goitre is no new-fangled notion. It was first recommended one hundred and thirty years ago, in 1831, by that delightful character, J B Boussingault – mining engineer, chemist, agronomist, traveller, *bon vivant* – probably the most peripatetic scientific Frenchman of his day who, on his travels in South America, noticed that the natural salt deposits, instinctively preferred by the peoples of goitrous districts in Colombia, contained most iodine.

General Therapy

But enough of iodine-deficiency goitre; let us move to another chapter in the iodine story – the ups and downs in its career as a general therapeutic agent, and as antiseptic and disinfectant.

Around the time iodine was discovered, French medicine was in the ascendant; traditional methods – bleeding, purging, the leech – were on the way out and yielding place to the first beginnings of experimental pharmacology. Pioneer in this new movement was François Magendie then at the height of his fame as an experimentalist. He it was who first put iodine into a pharmacopœia – in the year 1821.

In the first flush of enthusiasm for the newcomer, physicians and surgeons tested it and tried it for every conceivable pathological condition. The variety of diseases for which iodine was prescribed in the early years is astonishing – paralysis, chorea, scrofula, lacrimal fistula, deafness, distortions of the spine, hip-joint disease, syphilis, acute inflammation, gout, gangrene, dropsy, carbuncles, whitlow, chilblains, burns, scalds, lupus, croup, catarrh, asthma, ulcers, and bronchitis – to mention only a few.

Indeed, tincture of iodine, iodoform, or one of the iodides, was applied to almost every case that resisted the ordinary routine of practice; and between 1820 and 1840 there appeared a remarkable series of essays and monographs testifying to the extraordinary benefits to be achieved by this new and potent remedy.

In the Great Exhibition at the Crystal Palace in Hyde Park in May 1851 iodine and iodine compounds were publicly shown for the first time by ten pharmaceutical firms, including Hopkin and Williams of London, and Howards of Ilford – both still going strong.

Iodine preparations were urged and accepted into the prescribers' manuals of the day in rapidly increasing numbers. The first British Pharma-

copœia (1864) made a rigid selection of 14 preparations; by 1890, to choose a date at random, the 6th edition of Martindale's Extra Pharmacopœia sponsored 30 medicaments derived from iodine; the 'Iodine Centenary Volume' compiled by 'The Prescriber' in 1914 mentions 45 iodine preparations; by 1928 'Martindale' had extended its coverage to 128 iodine items; and, in an International Index published in 1956, and devoted exclusively to iodine pharmaceuticals, no less than 1,700 approved pharmacopœial names, proprietary names, synonyms, and alternative designations are alphabetically listed.

In the beginning, methods of applying iodine were scarcely less numerous than the variety of preparations available. The element was administered as vapour; as nascent iodine; in baths; in pills; in sweets; by inhalations; by irrigation, ionization and electrophoresis; in cigarettes; in tobacco, soaps, snuff, medicated matches, ointments, creams, hair-tonics, dusting-powders, suppositories, plasters, contraceptives, and even in an abortifacient.

Pharmaceutical literature of the nineteenth century is studded with iodine eponyms –Bryant's sherry; Churchill's caustic; Lugol's solution; Mandl's paint; Morton's fluid; Nourry's wine; Vanier's syrup; Whitehead's varnish – and so on. These men gave their names to the particular iodine preparations they invented and found useful. In French hospitals it was common practice to hang-up, on the crossbeams of the wards, strips of gauze steeped in iodoform (for all the world like old-fashioned fly-papers); and, in one Paris infirmary, the ward floors were strewn with dried seaweed in the belief that iodine emanations would pervade the atmosphere with beneficial effect.

Within a very short time of iodine's entry into medicine around 1820, ordinary people like ourselves, doubtless encouraged by the patent medicine vendors of the day, took to carrying little bottles of iodine hung round their necks, like amulets to charm away disease. Later, this practice fell into disrepute; but, oddly enough, was revived even in our own day.

Antiseptic and Disinfectant

First specific reference to the use of tincture of iodine in wounds appears to be that made in 1839 by John Davies, Surgeon to the General Infirmary, Hertford, whose 'Textbook on Surgery' included a special section on the application of tincture of iodine to lacerated, contused and punctured wounds. He did this, he says, 'to bring into general notice a remedy whose superior curative properties, as an external application, appear to be but little known to the Profession'.

The earliest recorded account of iodine tincture being applied to war wounds – wounds sustained on the battle-field – relates to the American Civil War.

On September 29, 1862, Colonel John B Gordon held the centre of General Lee's army at the battle of Antietam, or Sharpsburg. The first volley from the northern lines sent a ball through the calf of Gordon's right leg; soon after, another went through the muscles of his thigh; a third pierced his left arm, tearing asunder the tendons and mangling the flesh; a fourth ripped through his shoulder leaving a wad of clothing embedded in its track. Still, no bones were broken; but, while Gordon lingered in the firing line, 'with', as he says himself, 'but little of my usual strength', a fifth ball struck him squarely in the face.

Dr Weatherly of the 6th Alabama Regiment, in charge of medical arrangements, had the Colonel removed to a base hospital, and prescribed tincture of iodine to be painted on the wounds three or four times a day. The case was unpromising. Gordon's eyelids were greatly swollen; one eye was completely closed, the other almost so; his jaw was immovably clenched, and, to make matters worse, erysipelas had set in on the left arm.

Mrs Gordon, his wife, who nursed him – her name was Fanny, and she was then a beautiful girl of 25 – put a liberal interpretation on her instructions and painted the wounds, not three or four times a day, but, as Gordon himself says: 'I think three or four hundred times a day.' Fanny's diligence and devotion were rewarded. Her husband survived, outlived the war, became Governor of Georgia, a General, and Commander-in-Chief of the United Confederate Veterans. He died in 1904.

And so it came about that in every war throughout the remainder of the century, and indeed until the end of the 1914–1918 war, iodine tincture was declared a requisite in all field hospital stores and pharmacy waggons. Those of you who are old enough will remember the 'first field dressing' of 1914–1918, tucked into a little pocket on the left-hand inner-side corner of the battle tunic. It may fairly be said that at the beginning of the First World War most surgeons felt secure in the belief that a prompt application of a solution of iodine in spirit would suffice for the primary disinfection of a wound of moderate size; and that was why a small capsule of 2% tincture of iodine was included along with gauze and safety-pins in the 'first field dressing'.

Unhappily, the field conditions under which that war was waged inevitably gave rise to grossly infected wounds against which no chemical antiseptic was of any avail whatever, unless applied in excessive strength damaging to the living tissue. The technical reasons for this failure of iodine to

SOME LANDMARKS IN THE MEDICAL HISTORY OF IODINE

IODINE IN THE BRITISH PHARMACOPOEIA

	MONOGRAPHS	1st 1864	2nd 1867	3rd 1885	4th 1898	5th 1914	6th 1932	7th 1948	8th 1953	9th 1958	Addm. 1960
INORGANIC IODINE	ARSENIC IODIDE										*Dermatology*
	CADMIUM IODIDE										*Dermatology*
	HYDRIODIC ACID										*Expectorant*
	IODINE										*The Parent Substance*
	AQUEOUS IODINE SOLUTION										*Lugol's Panacea*
	SIMPLE IODINE SOLUTION										*Anti-Rheumatic*
	STRONG IODINE SOLUTION										*Antiseptic and Disinfectant*
	WEAK IODINE SOLUTION										*Antiseptic and Disinfectant*
	IODINE OINTMENT										*Counter Irritant*
	IODINE VAPOUR										*Respiratory Disease*
	IRON IODIDE										*Tonic and Alterative*
	IRON IODIDE SYRUP										*Tonic*
	LEAD IODIDE										*Dermatology*
	MERCURY IODIDE, GREEN										*Antisyphilitic*
	MERCURY IODIDE, RED										*Antisyphilitic*
	POTASSIUM IODIDE										*Alterative; Antisyphilitic; Expectorant; Diuretic; Etc.*
	SODIUM IODIDE										*Alterative; Antisyphilitic; Etc.*
	SULPHUR IODIDE										*Dermatology*
ORGANIC IODINE	CHINIOFON										*Amoebicide*
	DECAMETHONIUM IODIDE										*Anaesthesia*
	DI-IODOHYDROXYQUINOLINE										*Amoebicide*
	DIODONE										*Contrast Medium*
	EMETINE BISMUTH IODIDE										*Amoebicide*
	GALLAMINE TRIETHIODIDE										*Anaesthesia*
	IODOFORM										*Antiseptic*
	IODOPHTHALEIN										*Contrast Medium*
	IODOXYL										*Contrast Medium*
	IOPANOIC ACID										*Contrast Medium*
	LIOTHYRONINE, SODIUM										*Thyroid Hormone*
	PHENIODOL										*Contrast Medium*
	PROPYLIODONE										*Contrast Medium*
	THYROID, DRIED										*Thyroid Hormone*
	THYROXINE, SODIUM										*Thyroid Hormone*

Table 1

FROM FOLK MEDICINE
to
RATIONAL THERAPY

4th to 8th Century A.D.	INFUSION OF SEAWEED used to treat thyroid enlargement (goitre) by Chinese physician KE-HUNG (281-361). WANG T'AO (8th Century) lists 36 goitre prescriptions, 27 of which contain preparations of seaweed or other marine product.
1779	COVENTRY REMEDY. A secret remedy for goitre, now known to have contained "calcined spunge" brought a wide reputation and no small fortune to its owners, a doctor and an apothecary in Coventry. Details were published in 1779..
1811	DISCOVERY OF "A NEW SUBSTANCE" in seaweed ash by BERNARD COURTOIS (1777-1838). Not announced until 1813.
1813 27 Oct.	ARRIVAL of HUMPHRY DAVY (1778-1829) in Paris *en route* to Italy. Given a sample of the new substance; submitted it to experiment and "soon satisfied himself that it was a new elementary body analogous to chlorine."
1813 29 Nov.	FIRST PUBLIC ANNOUNCEMENT of COURTOIS' discovery made by C. B. DESÓRMES (1777-1862) and N. CLÉMENT (1779-1841) at meeting of Imperial Institute of France.
1813 6 Dec.	NAMING OF IODINE. J. L. GAY-LUSSAC (1778-1850) made known the results of *his* preliminary experiments, claimed the substance to be a new element and named it *Iode*.
1813 10 & 11 Dec.	CONTROVERSY. From Paris, HUMPHRY DAVY sent communications to The Royal Society of London and to the Imperial Institute of France seeking to establish that he, not GAY-LUSSAC, was the the first to prove iodine an element.
1816	FIRST MEDICAL USE? Writing in 1834, WILLIAM PROUT, M.D., F.R.S. (1785-1850) claims that he first used potassium iodide as a remedy for goitre in 1816.
1816	DISCOVERY IN SPONGES. ANDREW FYFE, M.D. (1792-1861), lecturer in chemistry, Edinburgh University and later professor of medicine and of chemistry at King's College, Aberdeen, demonstrated that iodine is a normal constituent of the common sponge.
1819	TINCTURE A GOITRE SPECIFIC. J. F. COINDET, M.D. (1774-1834) of Geneva, announced in 1820 to the Swiss Society of Natural Sciences his discovery, a year previously, that iodine tincture is a specific for goitre. COINDET is generally regarded as having been the first to introduce iodine into medical practice.

1819 SAINT THOMAS'S HOSPITAL. JOHN ELLIOTSON*, M.D., F.R.S. (1786-1868). Adopted potassium iodide as a remedy for goitre at St. Thomas's Hospital on the suggestion of Prout (*q.v.* 1816).

1831 IODIZED SALT FIRST RECOMMENDED. J. B. BOUSSINGAULT (1802-1887) noticed in 1825 that local salt supplies instinctively preferred by the inhabitants of goitrous districts in Colombia contained most iodine. He therefore recommended the iodization of cooking salt for goitre prevention.

1838 VIRTUE IN HARROGATE WATERS. *Dr.* JAMES INGLIS observed that goitre was common in the country around Harrogate but rare in the town itself. He ascribed this immunity to the presence of iodine and bromine in the Harrogate water.

1846 IODINE DEFICIENCY THEORY. Arguing from the successful therapeutic results obtained by COINDET (*q.v.* 1819) with iodine, J. L. PRÉVOST (1790-1850) of Geneva, in collaboration with his Italian colleague A. C. MAFFONI (1806-1878) first suggested that a deficiency of this very element in drinking water is the cause of simple endemic goitre.

1850 to 1876 FIRST CHEMICAL PROOF, by the French analyst G. A. CHATIN (1813-1901), that deficiency of iodine in air, water, soil and food is the primary cause of endemic goitre.

1895 DISCOVERY IN THYROID. Fundamental discovery that iodine is an invariable constituent of the normal thyroid gland was made by E. A. G. BAUMANN of Freiburg.

1913 to 1919 ISOLATION OF THYROID IODINE HORMONE. The iodine-containing principle of the thyroid gland was first isolated in crystalline form by E. C. KENDALL, M.D., Rochester, who showed it to contain 65 per cent of iodine, and named it *Thyroxine*.

1925 to 1930 SYNTHESIS OF THYROXINE. CHARLES R. HARINGTON, F.R.S., determined the chemical constitution of *Thyroxine* to be tetra-iodothyronine, devised means for its artificial synthesis, and pointed out the principal chemical features responsible for its specific physiological activity.

1952 TRIIODOTHYRONINE. Discovery by JACK GROSS and ROSALIND PITT-RIVERS that *Triiodothyronine* is present in the thyroid gland and forms a proportion of the circulating hormone, marks a new forward step towards eventual elucidation of precise chemical and physiological purpose of iodine within the animal body.

* *First President of the Royal Society of Medicine after its incorporation by Royal Charter in* 1834.

1. J. G. A. Lugol (1786-1851) originator of the aqueous solution of iodine (with KI) for treating scrofula.

2. Humphry Davy (1778-1829) wrote the first account of iodine in English.

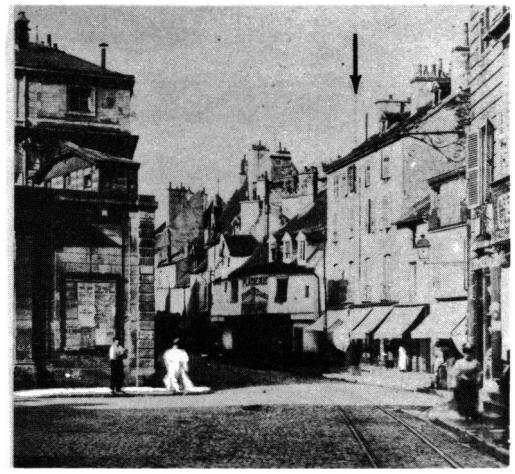
3. Gaspard Adolphe Chatin (1813-1901) first to show that deficiency of iodine in air, water and soil is associated with the occurrence of endemic goitre.

4. Eugen Baumann (1846-1896) discovered that iodine is an invariable constituent of the normal thyroid gland.

5. Thomas Wharton (1614-1673) described and named the thyroid gland in 1656.

6. Jean-François Coindet (1774-1834) introduced tincture of iodine as a goitre specific in 1819.

7. J. L. Gay-Lussac (1778-1850) proved iodine to be an element and named it.



8. The house in Dijon where Bernard Courtois was born.

(Photographs 1, 5, 7 reproduced by courtesy of the Wellcome Historical Medical Museum, London)

MATERIA MEDICA

1821 MAGENDIE'S FORMULARY. Iodine included for the first time in a prescribers' manual—the *Formulary* of FRANÇOIS MAGENDIE (1783-1855).

1821 IODINE TINCTURE INTRODUCED TO ENGLAND. *Sir* ANDREW HALLIDAY, M.D. (1781-1839) first to make detailed recommendations to the medical profession in England of the therapeutic uses and advantages of iodine preparations (especially the tincture) for diseases other than goitre.

1822 IODOFORM discovered by the French chemist, SÉRULLAS. Arguments for and against its medical efficacy continued throughout the 19th Century.

1829 INHALATIONS OF IODINE VAPOUR first recommended by *Sir* JAMES MURRAY, M.D. (1788-1871) for consumption, croup, catarrh, asthma and other respiratory diseases.

1829 LUGOL'S SOLUTION. J. G. A. LUGOL (1786-1851), physician in the Hospital of St. Louis, Paris, introduced the aqueous solution of iodine (with KI) for the treatment of "les maladies scrofuleuses". Wrote three memoirs on the subject.

1839 WOUNDS. First specific reference to the use of tincture of iodine in *wounds* made by JOHN DAVIES, surgeon, Hertford.

1851 POLAROID. WILLIAM B. HERAPATH, M.D. (1796-1868), professor of chemistry at Bristol Medical School, discovered that iodoquinine sulphate ("Herapathite") has light-polarizing properties. Forerunner of the modern *Polaroid.*

1862 BATTLEWOUNDS. Earliest recorded account of iodine tincture applied to wounds *sustained in battle* (American Civil War).

1864 IODINE finds a place in the 1st British Pharmacopoeia as *Linimentum Iodi* and *Tinctura Iodi.*

1865 ANTISEPTIC. A. A. BOINET, French surgeon, published his classic, *Iodothérapie,* in which he describes iodine as "un antiseptique, un désinfectant précieux."

1873 GERMICIDE. C. J. DAVAINE, French bacteriologist; first *knowingly* to employ iodine tincture as an agent for the destruction of infective organisms (anthrax).

1881 ROBERT KOCH (1843-1910). By common consent the greatest pure bacteriologist of his era. First to emphasize the germicidal potency of *aqueous* iodine solution.

1902 CATGUT STERILIZATION. M. CLAUDIUS, Danish bacteriologist, inaugurated a new safety era in surgery by recommending aqueous solution of iodine for the sterilization of surgical sutures. Aqueous iodine remains today the only effective *chemical* disinfectant of raw catgut.

1908 SKIN DISINFECTION. German surgeon, A. GROSSICH, was first to define and apply a rigid technique—known as the *Grossich technique*—for pre-operative skin sterilization by means of iodine tincture.

1910 "BRYANT'S SHERRY." Synonym for tincture of iodine. London surgeon THOMAS BRYANT* (1828-1914) wrote in 1910: "After 40 years experience I am pleased to express an opinion that it [iodine] is without doubt the best antiseptic that surgeons of the present day possess."

1916 "BIPP". RUTHERFORD MORISON, F.R.C.S. (1853-1939), famous Newcastle surgeon, originated *Bipp* (bismuth iodoform paraffin paste). "In *Bipp* we have discovered an antidote to true sepsis, and can leave dirty wounds undressed for a whole month."

1919 TRANSITION. ALEXANDER FLEMING (1881-1955) by exhaustive experiments at St. Mary's Hospital, London, in collaboration with *Sir* ALMROTH WRIGHT, proved conclusively that disinfection of an already infected wound by any then known chemical disinfectant (iodine among them) is not possible except at a strength destructive to body tissues. Ten years later (1929) *Sir* ALEXANDER FLEMING, F.R.S., discovered the first antibiotic, *Penicillin*, which virtually eclipsed purely chemical methods of disinfecting blood and body tissues.

1921 CONTRAST MEDIA. Advent of iodized poppyseed oil, first radio-opaque iodine contrast medium. Today (1961) iodo-contrast media account for more than 150 tons of iodine annually.

1939 END OF AN ERA. Last and perhaps greatest protagonist of direct energetic iodine disinfection of wounds was *Sir* LEONARD ERSKINE HILL, F.R.S. (1866-1952) director of research, St. John Clinic and Institute of Physical Medicine, London. Convinced iodine veteran of World War I, he returned to its defence on outbreak of World War II, extolling virtues of intensive iodine disinfection of wounds "in all their depths and ramifications". Views not accepted by the moderns. With him died finally the 1914-1918 war faith in the iodine "first field dressing."

1949 IODOPHORS. Iodine tamed. HERMAN SHELANSKI, M.D., of Philadelphia discovered that polyvinyl pyrrolidone and various surfactants solubilize iodine to form highly active complexes which do not sting or stain.

* *President of the Royal Society of Medicine*, 1898.

WORLD CONSUMPTION OF IODINE BY SOURCE OF PRODUCTION

YEAR	EPISODE	SOURCE	WORLD CONSUMPTION OF IODINE (10-year averages, excluding USSR.)				
			DECADE	SEAWEED	CALICHE	WATERS	TOTAL
					(METRIC TONS)		
1811	BERNARD COURTOIS: discovers Iodine in the ashes of	Seaweed					
1820-40	FRANCE, sole world producer	Seaweed					
1840	HAYES discovers Iodine in Chilean	Caliche	1840/49	31			31
1841	SCOTLAND begins production	Seaweed					
1855	JACQUELAIN: 1st extraction from Chilean	Caliche	1850/59	65			65
1860	IRELAND begins production	Seaweed	1860/69	90	1		91
1868	CHILE: first export of Iodine	Caliche					
1879	NORWAY begins production	Seaweed	1870/79	92	26		118
1888	JAPAN begins production	Seaweed	1880/89	72	164		236
1892	JAVA begins production	Waters	1890/99	100	345	2	447
1900	SOUTH AFRICAN WAR (1899-02)		1900/09	186	346	11	543
1914	WORLD WAR I (1914-18)		1910/19	200	627	31	858
1926	U.S.A. begins production	Waters	1920/29	177	626	53	856
1927	ITALY begins production	Waters					
1933	JAPAN begins production	Waters	1930/39	146	632	229	1007
1934	IRELAND and NORWAY cease production from Seaweed						
1936	SCOTLAND ceases production from Seaweed						
1938	JAPAN ceases production from Seaweed						
1939	WORLD WAR II (1939-1945)						
1940	JAVA ceases production from Waters		1940/49	42	889	348	1279
1950-59	CHILE, JAPAN, U.S.A., ITALY, sole	Caliche &	1950/59		1068	735	1803
1960-	producers today (excluding USSR.)	Waters	1960		>1200	>800	>2000

Table 2

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live up to preconceived ideas were exposed, at St Mary's Hospital, in classic experiments by Sir Almroth Wright and Alexander Fleming (later Sir Alexander Fleming of penicillin fame). And, as a result, iodine was withdrawn from the 'first field dressing' and from all official procedures by which wounds were treated in the Navy, Army and Air Force.

On the outbreak of the Second World War in 1939, one or two redoubtable diehards – I cannot but admire their tenacity – sprang to a renewed defence of iodine for swabbing wounds 'in all their depths and ramifications'. These efforts, however, did nothing to influence the contemporary outlook. All they did was to mark the end of what I call the energetic era of wound management.

To-day, there are only three major disinfectant roles for which iodine is fitted – and for which it has no equal. These are: rapid disinfection of unwashed intact skin; the sterilization of surgical catgut (iodine is the only chemical that will do this infallibly); and, thirdly, the emergency sterilization of infected drinking water.

Contrast Media

An entirely new chapter in the medical fortunes of iodine opened with the discovery of X-rays in 1895 – a development that put a new diagnostic aid into the hands of physicians, and brought undoubted advantage to iodine producers and pharmaceutical manufacturers alike.

Soon after their discovery, the suggestion was made that substances through which X-rays cannot pass might be introduced into the body to provide contrast shadows and so make organs and tissues visible on a radiographic film.

Iodine is a substance endowed with the power to stop X-rays. Moreover, it has other attributes desirable in the make-up of contrast media as they are called. The year 1921 saw the first contrast medium in use – an iodized oil named Lipiodol. By introducing a little of this into the lungs and air cavities, and then applying the X-ray, a shadow picture of the bronchial tree is obtained from which experts can readily determine whether all is well or something wrong.

Brain, arteries, the veins, kidneys, liver, gall-bladder, the reproductive organs, and almost every other bodily structure may be examined in this way. To-day, about 30 basic iodo-contrast media are available. But by the requirements of pharmacy firms, these same 30 are sold under something like 200 different proprietary brands and designations.

Chemotherapy

The turn of the century also saw the birth of a new chemistry – biochemistry – which brought with it the gradual ascendancy of rational over empirical modes of treatment. Broadly speaking, chemotherapy, or replacement therapy, is the intelligent use against disease of these very drugs, extracts and principles which the living body continually manufactures within itself to keep itself alive, and whose deficiency or absence through some mechanical breakdown gives rise to disease. For example: insulin *versus* diabetes; liver extract *versus* anæmia; cortisone *versus* adrenal deficiency and a whole lot else; and, as we have already discussed, thyroid extract and thyroxine *versus* thyroid abnormality.

This broadening and deepening outlook on therapeutics is clearly reflected in the changing composition of official and non-official pharmacopœias. The old, and to us perhaps rather crude, materia medica – predominantly inorganic in kind and content – is giving place to a vocabulary of finer pharmacological texture – largely organic.

Not unnaturally, iodine has shared in this progressive movement, and Table I (*see* insert) shows how the British Pharmacopœia of modern days has taken on an entirely new look so far as iodine is concerned. Since 1864, there have been nine 'B.P.s' plus an addendum in 1960. Horizontal lines in colour mark the stages at which various iodine preparations were introduced, and the length of their survival as accepted therapeutic agents.

If one separates the inorganic monographs from the organic, that is, the simple from the complex, the upper and lower halves of the table – and take, for example, the 3rd 'B.P.' (1885) – one finds in it 13 inorganic iodine preparations and only one organic item, iodoform. Seventy-five years later (1960) only 6 basic inorganic, and 12 organic items are seen – an almost complete reversal.

On top, in red, are the parent substance, the strong and the weak tinctures, and potassium iodide – all with a record of one hundred years. Lugol's solution (5th on the list, top half) had a first innings of twenty years, was removed for thirty years, but was reinstated in 1948, and is still 'not out'.

Below, the organic members of the team are all comparative newcomers, and, as we have noted, are used for therapeutic purposes wholly different from those customary in former times. The switch in usage has been from skin disease,

venereal disease, and general tonic purposes (top half) to contrast media, thyroid therapy and the control of specific tropical diseases by organics such as chiniofon and iodo-hydroxyquinoline (lower half).

So much for the pharmacy and medicine of iodine.

Sources and Consumption

To occupy the time left at my disposal I would like to make a very brief historical note on the commercial sources of iodine, and upon world consumption as it was in the beginning and as it is today.

Table II (*see* insert) shows the average annual world consumption of iodine, decade by decade, for one hundred and twenty years from 1840 to 1960; and the amounts contributed to this consumption by the three great producing sources – seaweed (in green), Chilean *caliche* (in red) and underground waters (in blue). The totals are in metric tons; no data exist prior to 1840.

Seaweed, in which iodine was discovered, remained the only commercial source until Chile entered the field in 1868. Chilean iodine is obtained as a by-product during the elaboration of Chilean nitrate of soda from the raw material called *caliche* which occurs in vast natural deposits in Northern Chile.

From 1868 onwards, the Chilean share of the world iodine market gradually matured and overtook the seaweed share around 1880/1890. As a consequence, the seaweed contribution to world needs – provided mainly by France, Scotland and Japan, and with a zenith of 200 tons per annum in the decade 1910/1919 – gradually declined and fell to zero at the end of the Second World War. No seaweed iodine is produced to-day anywhere in the world, unless it be in Russia, which is doubtful.

In 1892 a new and powerful impact struck iodine commerce when workable quantities of the element were found in certain underground waters – mineral springs and natural brines, particularly in oil-field areas.

Java (in 1892) was the parent of this enterprise; California followed in 1926; Italy in 1927; and Japan in 1933. With the final elimination of all seaweed production in 1945, world needs are now supplied entirely from Chilean *caliche* and from underground waters in Japan, the United States, and Italy. To-day, world consumption lies between 2,000 and 2,500 tons – four times more than at the beginning of this century and twenty times more than one hundred years ago.

The figure mentioned excludes Russia and covers all fields of usage. Broadly speaking, 50% of the total is used for medical purposes; 30% goes into technical industry; and the remaining 20% into veterinary medicine and agriculture. This means that 1,000 to 1,200 tons are absorbed every year into pharmaceutical and medical use; and of this quantity 60% is converted and used in the form of potassium iodide.

These figures are near approximations. It is exceedingly difficult to obtain reliable statistics on the end-usage of iodine at any given moment of time. All sorts of unexpected factors and circumstances may intervene to upset one's calculations as, for example, when during the last war an exceptionally heavy and persistent demand arose in certain neutral countries for an iodine preparation called Entero-Vioform, sought ostensibly for the treatment of parasitic disease. In fact, this was none other than an attempt to smuggle iodine into Germany where supplies of crude material were non-existent. A more interesting irregularity occurred in the United States around the year 1927 when the iodine industry was surprised to notice an enormously increased demand for the alcoholic tincture of iodine. This was the era of prohibition in America, and it soon became apparent that the unprecedented sales of alcoholic iodine tincture were not for legitimate medical use, but simply to recover alcohol for 'bootlegging'.

Special legislation was introduced to control this nefarious trade, but not before 50 tons of iodine had been illegally diverted – representing approximately one and a quarter million litres of absolute alcohol.

What of the future? Who can tell how the reputations of iodine to-day will stand one hundred years hence? To venture an opinion, based, as it can only be, on the events of the past, I can only say that the process of research, revaluation, reappraisal, refinement, will go on, and that in the year 2061 some iodine merits that enjoy contemporary favour will plainly appear ephemeral, while new merits as yet hidden from us will assuredly have declared themselves. We may safely leave it to our successors to share the surprises that time has yet in store.

The 8-page insert accompanying this paper contains Tables I and II referred to in the text, a list of important dates in the medical history of iodine, and photographs of several of the great personalities who have helped to make the iodine story.