The Metabolism of Iodine Compounds*,†

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THE nonmetallic element iodine belongs to the so-called group of "halogens," of which chlorine, bromine, and fluorine are the other outstanding members. In its solid form iodine occurs as heavy shining crystalline scales, which are blackish gray in color. When heated, however, these sublime to yield a beautiful reddish violet vapor. Even the solid scales or the alcoholic tinctures have a pungent acrid odor which is characteristic. The atomic weight of iodine is 126.9, and its molecular weight twice this value. Its atomic number is 53. It occurs only in traces in most natural substances, but is especially concentrated in sea water and certain mineral waters, in marine plants and corals, and in sea food such as oysters. Its salts are commonly found in cough medicines. It was discovered in 1811 by Courtois in France. It can be prepared from the ashes of kelp (i.e., seaweeds) or from crude Chile saltpeter. In its elementary form it colors starch or starched objects a deep blue. Recently, under the auspices of the Atomic Energy Commission, a copious supply of radioactive iodine has become available. In the process of physical decay, for example, each atom of the eight-day isotope,[1] I^{131}, yields both beta and gamma radiations.

THE DISCOVERY OF IODINE

If one considers how iodine happened to be discovered, it seems that two major situations lie back of this important finding. The first of these was contemporary, namely, the ambition of Napoleon Bonaparte and his need for gunpowder. The second of these was more fundamental, namely, Nature's discovery, millions of years ago, that iodine and bromine (both halogens) would form organic compounds which were useful in the constitution and function of primitive organisms. About 1811 these two circumstances came into conjunction and the result was the discovery of a new element.

By 1810 the continued drain of Napoleon's campaigns upon the natural resources of France, together with the limitation of sources of niter (saltpeter) from other parts of the world because of the blockade, led to a concerted effort in France for the exploitation and development of new sources of nitrate. Temporarily a profession of salpêtriers had sprung up, devoted to the production of nitrate from organic materials. Originally potash was used as a source of the potassium but as wood became scarce other materials were tried. Furthermore, the production of ammonia and nitric acid from decaying vegetable and animal sources became an increasing problem. Consequently, certain of the salpêtrières turned to seaweed as a raw material, and particularly to the variety known as "le varech." The story of the corrosion of his copper-lined vats by Monsieur Courtois (1), (published in 1812), followed by the observation that the distillate from sulfuric acid yielded violet-colored fumes, is familiar to all of you, I am sure. The finding was checked and corroborated by the eminent French chemist Gay-Lussac (2), who named this purplish element "violet" in Greek, after the humble but beautiful flower, *'Ιον*, to which it was likened—i.e., *'Ιο-ειδής* or *'Ιώδης*.

For thousands of eons Nature had been utilizing this element in the construction of primitive organisms. Possibly the high prevalence of iodine in sea water relative to the waters of the land had something to do with this. At any rate, together with bromine, iodine is a prominent constituent of the sea fans, corals, and sponges. In particular, the species *Gorgonia* is replete with iodine. In general, many marine plants contain more iodine than does terrestrial vegetation and among these are the large brown forms called kelp and various other seaweeds. The same holds true of the ash of these plants, when burned. Thus it came about that when Courtois' factory (salpêtrière) turned to "le varech" as a starting material in the manufacture of niter he unwittingly brought this unknown element into the picture.

Because of man's greater interest in mammalian physiology than in plant physiology, we know today much more about the behavior and function of iodine in mammalian organisms than in the corals. Among others, Professor Werner Bergmann (3), of Yale in recent years has studied the participation of organically bound iodine and bromine in the structure of sea organisms. This interest is a traditional one at Yale because Wheeler and Jamieson (4) as early as 1905 synthesized iodo-gorgonic acid, previously isolated by Drechsel (5) from certain marine forms (*Gorgonia*) and identified it as diiodotyrosine.[2] In 1895 Baumann (6) had discovered the presence of iodine in the human thyroid

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and shortly thereafter had assumed that diiodotyrosine was present. Subsequently Oswald (7) tried for many years to isolate it from mammalian thyroid tissue. The actual identification was not made until 1930 by Harington and Randall (8), but at that late date the isolation was merely a necessary confirmation of what seemed to most investigators to be a foregone conclusion. Of course, the inquisitive scientist, on learning these facts, will at once begin to wonder how iodine in sea water can be built into an organic compound within organisms, and what role organically bound iodine plays in the metabolism both of plants and of animals. From the standpoint of the pharmaceutical chemist and the pharmacologist these findings are of basic interest, because a knowledge of the biochemistry of natural iodine compounds inevitably will pave the way for the development of useful synthetic products.

THREE CHIEF CATEGORIES OF IODINE IN METABOLITES AND DRUGS

For purposes of classification and for convenience in cataloguing the main facts about iodine metabolism in relation to drugs, it is useful to divide these materials into three chief groups. These are as follows:

Iodine in a High State of Potential Biochemical Activity—This class would include chiefly elementary iodine itself, and solutions and tinctures of elementary iodine. It would also include some of the complexes or compounds of iodine, such as that produced with glycine, nitrogen tri-iodide or the starch-iodide complex, in which a peculiar type of chemistry governs the behavior of each compound.

The Iodide Ion in Various Media.—From the physiological point of view, iodide itself is the starting point of nearly all natural events. The ion exists free in sea water and in the blood stream of man. When iodine-containing medication is administered to animals or to man, ordinarily a large part of the iodine in organic compounds ends up as iodide, even though it was organically bound at the start. When sea water or natural body fluids are evaporated, the great preponderance of sodium leads to the isolation of the iodide largely in the form of sodium iodide. However, in the organism, the alkali salts of hydriodic acid are carried largely in dissociated form. Therefore, we need not concern ourselves with physiological distinctions between potassium and sodium iodide under ordinary circumstances.

Organically Bound Iodine.—In addition to those compounds containing iodine which exist in natural sources, there is now a host of iodine-containing compounds which have been used for physiological investigation or for therapeutic purposes. A few of these are of natural origin and their properties are part and parcel of the biochemistry of life. Thyroxine and thyroglobulin are instances of this type. A large number of compounds are known, however, which are man-made and are utilized for specific purposes. This phase of pharmaceutical chemistry is only in its infancy. Indeed, the properties of these compounds are so manifold and interesting that doubtless much more work will be done in the development of interrelated and extrapolated chemical formulas in the future.

Iodine in a State of High Potential Activity

At the moment the chief pharmacological interest in elementary iodine, which to the biologist appears to represent a high state of potential biological activity, is based upon its ability to combine with protein. Its combination with the constituent amino acids of protein probably involves chiefly three types of reaction. The first is the iodination of tyrosine which has been studied by Harington (9). The second, studied by Johnson and Tewkesbury (10), is the production of thyroxine. This process goes on even though the tyrosine is bound into the peptide chain of the proteins, as demonstrated by the studies of Muus, Coons, and Salter (11), and of Turner, Williamson, and Reineke (12). This combination of elementary iodine with protein has been applied in three general ways. First, active substitutes for thyroid medication have been produced, which will relieve the human disease known as myxedema. Such material has been tested in milch cows for its ability to increase milk production, and in hens to increase egg production. Secondly, the reaction has been employed in scientific studies to label foodstuffs and antibodies, much as fat was formerly distinguished by its iodine content in feeding experiments. Finally, the combination with protein has been applied widely for its effect on bacteria and parasites.

Apparently when this reaction occurs, many bacterial and mammalian proteins or enzyme systems are no longer able to function naturally within the cell protoplasm. Probably frank coagulation of the protein does not necessarily occur until a further reaction supervenes, namely, the iodination of histidine as described by Li (13), and by Blum and Grützner (14). By this time, drastic oxidative processes have also occurred; leading, first, to the formation of thyroxine or close derivatives thereof (15, 16) and, secondly, to the splitting off of sulfur from the cysteine and methionine components, so that the protein becomes obviously denatured. Once this action, which is truly violent in a biological sense, has occurred, the subsequent fate of the iodine is the fate of the individual iodinated components of the protein.

Although elementary iodine has enjoyed an extensive vogue as a bactericide, obviously its use will be limited by the fact that it does not distinguish between bacterial and mammalian protein. In a sense, therefore, it may be regarded as a chemical cauterant which simply coagulates all living material within its sphere. The end products of its action must be broken down and dissolved or sloughed off. Consequently, the deep ulcers formed after the injudicious use of elementary iodine delay healing, because often the wound must heal by granulation and the formation of scar tissue. To avoid this mishap, in recent years attempts have been made to moderate and control the action of the element—either by the adjustment of the ointment base in which the iodine is suspended or by the formation of iodine-buffer systems, notably with glycine. The actual chemistry involved in this reaction is still not very clear, but it rather resembles the oxygenation of hemoglobin, in that such glycine-buffer complexes slowly and reversibly yield elementary iodine which becomes available as each preceding moiety is utilized. This feature is

certainly a characteristic buffer action. Moreover, more dilute tinctures of iodine have become standard, in order to assure a milder action. Besides, the routine surgical practice of washing off the excess with alcohol is being learned by millions of anxious mothers.

When such mild complexes or dilute solutions of elementary iodine are ingested, they combine rapidly with the food or with the mucus and epithelial lining of the alimentary canal to form iodinated protein *in situ*. If the latter combination is particularly extensive, of course irritation of the gut occurs, which is identified by nausea and vomiting or even by bloody diarrhea. Ordinarily, however, such situations occur only after suicidal attempts or accidents.

The laity is apt to attach too much importance to this corrosive effect without due recognition of the concentration involved. For example, one or two drops of tincture of iodine in a glass of water are tolerated easily by people undergoing treatment for goiter of various types, particularly if the iodine-containing water is sipped during meals. Furthermore, the use of iodate, IO_3^-, in the making of bread has created undue alarm. In the ordinary processes in which iodate has been used for bread making, a very small concentration is mixed with a huge excess of vegetable protein and milk. Long before the doughy mass is ready for the oven, this iodine-containing oxidizing agent will have been reduced and combined to a large extent with the vegetable and animal proteins. That portion which escapes combination with the protein, of course, will persist as iodide. If any trace fails to react within the first few minutes, it will surely be decomposed under the conditions of baking. Failure to appreciate the instability of the higher oxidation forms of iodine in the presence of organic matter has led to a great deal of useless apprehension and unfounded fear. Many years ago Cohn (17) and others (18) even administered dilute solutions of potassium iodate in water directly to dogs, and found that the resulting metabolic story was primarily that of simple sodium iodide in equivalent concentrations.

Iodine and Skin

It is often forgotten that elementary iodine penetrates the skin and is absorbed into the circulation. Probably the oily sebaceous glands and the sweat glands facilitate this assimilation. Most of the absorbed material is converted into iodide and enters the blood stream, to be distributed to all parts of the body. In former times, goiters used to be treated by local applications of tincture of iodine or of milder iodine-containing ointments to the neck. There is no question that the therapy was successful. The amusing fact, however, is that the assimilated iodine first had to be carried by the blood to the lungs and the heart; and then pumped back through arteries to the thyroid gland before it could relieve the thyroid swelling. Indeed, even the pituitary gland within the skull was involved in the disease and its relief.

The Pharmacology of Iodide

From the physiological point of view, iodine metabolism in the normal man starts with the inorganic form, iodide. The same, of course, is true of the corals and sea fans. In the tissue juice of these sea organisms free iodide ion circulates by diffusion, whereas in the blood of man it is pumped about in the circulation of the blood. In both cases, however, as shown by the fact that it is uniformly distributed throughout the interstitial fluid, and with minor exceptions and reservations, it probably also permeates uniformly the water in the cell sap. Studies by Wallace and Brodie (19) have shown that at concentrations which are well above physiological levels this picture also holds.

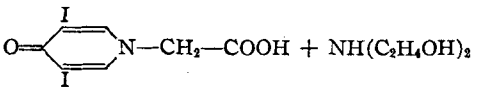
Of course, the old observation of Pliny (20), "Tales sunt aquae quales terrae per quas fluunt," is true in the case of men and dogs or other domestic beasts. Dr. David Marine, an eminent pioneer in the study of thyroid disease, was once late for his lecture in the Middle West because he stopped to examine the goiters of three dogs he met. In the backwoods of Michigan or even in the Connecticut valley, the iodide circulating in the blood is almost at the vanishing point, namely, at about half a microgram per cent. On the other hand, the good Catholics in Boston, Mass., who live close to the sea and who eat fish twice a week—not to mention the excellent oysters to be obtained in the heart of that city—carry in their blood streams a higher concentration of iodide in evidence of their piety, namely, possibly two or three micrograms per cent. At the other extreme, the victim of tertiary syphilis a generation ago who was treated rigorously with potassium iodide by his physician, might have a plasma concentration of several hundred micrograms per cent.

In my monograph (21) I have delineated four arbitrary but useful levels of iodine intake. These are: (*a*) the natural level of iodine intake; (*b*) the prophylactic level against simple goiter; (*c*) the therapeutic level (against exophthalmic goiter with hyperthyroidism); and (*d*) the fibrolytic level. In the last category are included various treatments which the older clinicians have used and which were denounced as leading to "iodine debauchery" by Veil and Sturm (22). Indeed some of the victims of this heroic sort of therapy showed extreme emaciation, not to mention the coryza, general catarrh, and pustular acne characteristic of iodism. Before better therapy became available, however, many a syphilitic patient saw his gumma melt away and many a farmer's actinomycotic jaw was relieved by such therapy. It has achieved its bad name because, as they used to say in Germany, "Wenn man weiss nicht wie so, warum . . . Dann gibt man jod kalium." In other words, when you don't know what else to do, give the poor patient some potassium iodide.

Obviously, whenever iodine in the first category (that of high oxidation) is administered, one is also administering iodide ions indirectly, because such compounds rapidly break down to form the inorganic form, i.e. iodide. This is true even when cutaneous ointments are given or when tincture of iodine is painted on the skin. Indeed even the carrying about of little amulets containing elementary iodine, so common in the French Midi a century ago, can lead ultimately to a very definite absorption of iodine or of iodide through the oily sebaceous glands, and goiter may actually be prevented by such superstition. Its abuse, however, led to legislation in the French Midi against its general use without proper medical supervision.

Organic Compounds of Iodine

Finally, there are a number of compounds of miscellaneous character in which the halogen is incorporated into an organic radical with the purpose of influencing its properties and pharmacological utility. The number of such compounds is growing and obviously we cannot hope to mention them all today. In our time, they have perhaps been brought to greatest recognition through the researches of Evarts Graham (23), and his colleagues (24), who developed a group of compounds which were radiopaque. For example, tetraiodophenolphthalein derivatives were found to be concentrated by the liver, excreted through the biliary tract, and ultimately concentrated in the gall bladder. The four iodine atoms in the molecule rendered solutions of this substance dense enough to cast a differential shadow when illuminated by X-rays. Consequently, it was possible to visualize the gall bladder and to detect cholesterol stones by virtue of their lighter density. In similar fashion Homer Smith (25) and his colleagues have used other iodo-compounds (Table I) to study renal clearance. A number of these have been widely used under the names of "Uroselectan," "Skiodan," "Diodrast," and several other proprietary names. Combined with creatinine—or, better, xylose—clearances, these substances are useful in measuring the mass and function of the tubules of the kidney, and have contributed considerably to our understanding of renal function and the fundamental background of Bright's disease. In addition to their use by intravenous injection, such compounds may be employed in local instillations. An example is Iodopyracet, U. S. P. (I), i.e., "Diodrast," which can be used to visualize the pelvis of the kidney, the bladder, and other urinary passages. A sterile aqueous solution of the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid is made at about 35% concentration. Because the dry salt contains about 62% of the dense element iodine in combination, as shown in formula I, it casts a definite shadow in the X-ray picture.



Iodopyracet, U. S. P.

(I)

Several such compounds are now available. Among these are Methiodal Sodium with about 52% iodine; Neo-Iopax also with 52%; Hippuran with approximately 36%; and Iodoalphonic Acid with about 51% iodine. In modern times this genito-urinary application has become relatively more important than the original gall bladder test of Graham. Both procedures, however, illustrate the fundamental feature of differential concentration and excretion at certain sites in the body. In both cases, also, it is the density of the inherent iodine atoms which renders the substances useful.

In other situations, the halogen has been introduced into the molecule for the purpose of influencing its over-all properties, both chemical and biological. It will be recalled that some of our best antimalarial drugs and antibiotics contain chlorine in organic combination. It used to be thought that these substituted halogen atoms exerted their influence by yielding free chlorine within the cell protoplasm. Indeed, the same theory was held until within a decade for the action of mustard gas as used in gas warfare. It would now appear that this theory is too naive and that the role of the chlorine in the organic molecule is much more subtle. The same may be said of many organic compounds of iodine. It is true, of course, that certain compounds like iodoform do yield a certain amount of iodide within the body and probably also (in the presence of protoplasmic oxidase systems) a trace of iodine or hypoiodous acid as a consequence of their degradation. In general, however, this would seem to be a minor and probably incidental feature of their metabolism within the mammalian organism.

TABLE I.—ORGANIC IODINE COMPOUNDS IN RENAL CLEARANCE

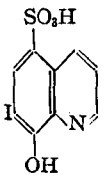
[From Smith, H. W., and Ranges, H. A., (25)]

Type of Compound		Average Inulin Clearance Ratio	Tm[a] mM. per Minute	Per cent Free[b]	Approximate Per Cent Depression Effected by 1.0 mM. per Liter in Plasma: On Self-clearance	Approximate Per Cent Depression Effected by 1.0 mM. per Liter in Plasma: On Simultaneous Phenol Red Clearance
Diodrast.....	3,5-Diiodo-4-pyridone-N-acetic acid	6.0	0.3	72	50	85
Hippuran	Sodium ortho-iodohippurate	5.4	0.6	30	25	80
Iopax.....	Sodium 2-oxo-5-iodopyridine-N-acetate	5.0	0.2	56	65	75
Neoiopax.....	Disodium N-methyl-3:5-diiodo-4-pyridoxyl-2:6-dicarboxylate	1.2	0.01	74	25	55
Skiodan.....	Sodium mono-iodomethane sulfonate	1.2	>0.1	82	±5	±5

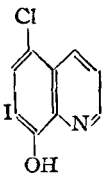
[a] The maximal rate of tubular excretion. The data on diodrast and hippuran are quoted from Smith, Goldring, and Chasis, *J. Clin. Investigation*, **17**, 263(1938).

[b] Per cent of total dye filterable at a total concentration of 1.0 mg. per cent, in human plasma containing 4 per cent albumin.

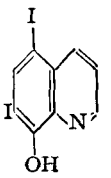
As examples of this total-molecule effect certain drugs used against the organisms of amebic dysentery may be cited. These include Chiniofon, U. S. P. (7-iodo-8-hydroxy-quinoline-5-sulfonic acid) (II); Vioform, N. N. R. (5-chloro-7-iodo-8-hydroxy quinoline) (III); and Diodoquin (5,7-diiodo--8-hydroxy quinoline) (IV). Their respective chemical formulas appear below:



(II)



(III)



(IV)

The compound last named is much less toxic than Vioform, which contains one chlorine atom instead of an iodine. The danger of gastrointestinal irritation and of liver damage is definitely less. Nevertheless (when combined with emetine from ipecac) it has produced very satisfactory therapeutic results (26). Obviously, in this instance, the important iodine atom has merged its identity with that of the whole molecule, and one cannot claim that this effect is due only to elementary iodine.

Of course there are compounds which are effective on topical administration because they slowly evolve elementary iodine locally. Thymol iodide, the dusting powder known as "Aristol," is one of these. On the other hand, the local effect of Vioform in treating infection with *Trichomonas vaginalis* may well be unrelated to free iodine. It is interesting that the official Iodine Tincture of U. S. P. XIII, once known as "mild surgical tincture of iodine," contains only 2% of free iodine. The "strong iodine tincture" of N. F. VIII is much more likely to produce irritation and blistering of the skin because it contains 7% of free iodine. This difficulty could usually be avoided if the excess of iodine were always washed away with 70% alcohol after a minute or two of action. Modern ointment bases act somewhat similarly by withholding the elementary iodine from the skin or ulcer, at least temporarily, or by paying it in slowly.

DEGRADATION TO IODIDE

Most of the compounds now available in all three of the categories just surveyed begin to decompose into iodide soon after they are admitted into the mammalian body. This feature holds even when they are still in the alimentary canal and not strictly *within* the organism proper. How this degradation occurs is a matter of some interest, because the persistence of action of drugs containing iodine (and in which the iodine atom is an essential component) depends in part upon the rate of decomposition. Many pharmaceutical chemists and pharmacologists do not appreciate the fact that whenever an iodine-containing organic chemical is administered for therapeutic or diagnostic purposes, iodide is simultaneously being administered in potential form. This is true not only for substances such as sodium iodate (*in*organic in nature) but also for volatile organic compounds like ethyl iodide which is sometimes used for the determination of the circulation rate. It is also true of thyroglobulin and iodocasein, and for such classical compounds as iodoform. All of these substances begin to release iodide soon after their injection or ingestion into the animal organism, or even on contact with raw flesh. This decomposition may occur through bacterial action or by simple hydrolysis within the alimentary canal. A good deal of decomposition of ingested material occurs, however, in the liver after absorption. Undoubtedly once a steady state of metabolism has been established, the iodine-containing compounds are degraded by the tissues at large, including the blood.

Iodases.—Every now and then some investigator revives the problem of iodases—namely, enzymes specifically concerned with the fixation of iodine in organic molecules and, conversely, with the removal of iodine therefrom. Years ago, Blum (27) pointed out that such catalysts must exist in the blood stream. Recently, Curtis and his colleagues (28) have shown that when iodide is added to blood plasma, after a time the iodide is incorporated into the plasma protein by some sort of linkage not yet understood. This combination does not occur if the blood is heated or treated with a protein-coagulant like alcohol or acetone. Of course it is known that compounds like thyroxine are readily decomposed by hydrogen peroxide and by catalysts such as spongy platinum or palladium saturated with hydrogen. Therefore it is conceivable that some decomposition of iodo-compounds occurs as a non-specific effect of reducing agents or of oxidation-reduction systems such as peroxidases. Obviously this subject needs much more study.

An interesting beginning has been made by Keston (29), who showed that the xanthine oxidase of milk could convert iodide into diiodotyrosine and from this small amounts of thyroxine were formed. The effect of thiouracil and related goitrogens in the thyroid gland strongly suggests that specific enzyme systems exist which build iodine into diiodotyrosine and then into thyroxine. Indeed by the use of successive goitrogens like thiocyanate and thiouracil it is possible to present evidence, as I have done (30), that the iodide ion is first trapped by an iodinase system, which is then acted upon by a periodase system to form diiodotyrosine. Of course this *schema* as shown in Fig. 6, is quite analogous to the iodase systems which are classically known to guide cellular oxidation. In the latter example, however, atmospheric oxygen is first trapped by an oxygenase and the resulting complex is then acted upon by a peroxidase to liberate the equivalent of nascent oxygen.

Inasmuch as enzyme systems act in either direction according to thermodynamic conditions, it is not necessary to assume that specific biological systems exist both for the building up and for the breaking down of organic combinations of iodine. Nevertheless it is quite possible that in the tissues no such highly developed iodinase system exists as in the thyroid gland. Indeed it is even conceivable that the enzymes or enzymic systems which break down thyroxine and other iodo-compounds in cells are no different than those which decompose various metabolites which do not contain iodine. Ultimately a careful study of these enzyme systems in tissues must be made from the standpoint of the persistence

of iodine-containing drugs within the body. Such knowledge will doubtless lead to the development of more stable drugs, the composition of which will continue unaltered in the body for longer periods than now encountered.

THE FATE OF IODIDE

The Thyroid Route.—When iodide is admitted into the body, it is distributed rapidly through all body fluids. It is probably absorbed even through the stomach wall. When administered through a stomach tube or through a duodenal catheter, it appears in the blood stream within five to ten minutes and even in the saliva within about fifteen minutes. If the alimentary canal is empty, most of the iodide is absorbed within an hour. If food is present, absorption is slower because some of the dissolved iodide is retained in the chyme. Once the iodide ion is admitted to the circulation, it is distributed rapidly throughout all body water. Normally the concentration is of the order of one microgram per cent, but when medication high in iodine is administered, the concentration in body fluids may mount to one or more *milligrams* per cent, i.e., over a thousand times the usual value. Within an hour or two it will come into equilibrium with the spinal fluid and soon the concentration in that liquid will be the same as in the plasma water. This does not mean that the *total* concentration of iodine in spinal fluid is equal to that of plasma. Actually, spinal fluid contains only about one-fifth of the total iodine of the human plasma, because most of the iodine normally in human plasma is *organically* fixed. So uniform is this distribution of iodide in body fluids that radioactive tracer iodide has been used to measure the volume of body water. In Table II, for example, are shown recent observations in men made by Keating and Albert at the Mayo Clinic (31). The values for the distribution-volume are quite anlogous to those obtained by other methods. Indeed they are sharp enough to discriminate between hypo- and hyper-thyroid patients as compared with normal men.

After an organic compound of iodine is administered, and as this material breaks down in the alimentary canal or within the blood stream or elsewhere, iodide is paid out progressively into the circulation and distributed through the body fluid. Therefore, whenever an iodine-containing drug is used, the fate of iodide itself immediately is involved in the total picture.

Once the iodide has entered the general systemic circulation, its subsequent history involves four major channels. From the circulation a goodly proportion of the iodine is taken up by the thyroid gland, which is a marvelous iodide trap. The activity of the thyroid in this respect can be measured by the use of tracer iodide, and Keating and Albert (31) have proposed the concept of "thyroid clearance" to indicate the volume of plasma that hypothetically could be freed completely of iodide per minute. Between the normal and the hypothyroid man there may be over a tenfold increase in this clearance rate. When amounts of iodide less than a hundred micrograms are administered to man, the proportion of the iodide which ends up in the thyroid may be over 70% in hyperthyroidism and frequently over 40% in normal man. As larger and larger doses of iodide are given, however, less and less is trapped by the thyroid gland, which soon becomes saturated.

Renal Clearance.—Competing with thyroid clearance is the "renal clearance" which accounts for the major portion of iodide excretion, as shown in Fig. 1. This iodide clearance is measured in precisely the same way as urea clearance has been measured for decades in accordance with the equation proposed by Van Slyke while at the Rockefeller Institute (32):

$$\text{Clearance} = UV/B$$

where U is the concentration of iodide in the urine, B the concentration of iodide in the blood, and V the volume of urine produced per minute. Obviously the thyroid and the kidney compete with each other in the removal of iodide from the circulating plasma. Indeed, my former associate, Dr. Douglas Riggs, now at Harvard, has found that a normal man "clears" free of iodide about 40 ml. of plasma per minute (33). If the thyroid is hyper-active, as in exophthalmic goiter, it will predominate over renal excretion at least for a short time. Similarly

TABLE II.—APPROXIMATE VOLUME OF DISTRIBUTION OF INORGANIC IODIDE

[From Keating, A. R., and Albert, A. (31)]

Group	Cases	Approximate Volume of Distribution: Method C,[a] Liters	Approximate Volume of Distribution: Method D,[b] Liters	Mean of Individual Differences, Liters	Volume by Method D, Cc. per Kg.
Exophthalmic goiter	16	32.0 ± 1.8[c]	31.2 ± 2.2	−0.7 ± 1.7	530 ± 43.8
Euthyroid	6	25.9 ± 2.9	26.0 ± 3.5	+0.07 ± 0.8	350.2 ± 38.6
Myxedema	6	24.4 ± 2.7	23.9 ± 3.1	−0.5 ± 1.6	352.8 ± 35.9
Adenomatous goiter with hyperthyroidism	3	25.3 ± 4.7	22.1 ± 6.4	−3.2 ± 0.5	340.0 ± 39.3
Adenomatous goiter without hyperthyroidism	3	20.9 ± 1.9	20.9 ± 2.7	−0.07 ± 1.0	316.0 ± 50.6

[a] Method C = Volume estimated by taking the value $\frac{1}{C_0}$, the reciprocal of concentration.

[b] Method D = Volume estimated by taking the value $\frac{\text{Clearance}}{Quf \times r} \times 60/1000 \times 100$. The mathematical symbols are explained by Fig. 1.

[c] The values given are the means and standard errors of the means.

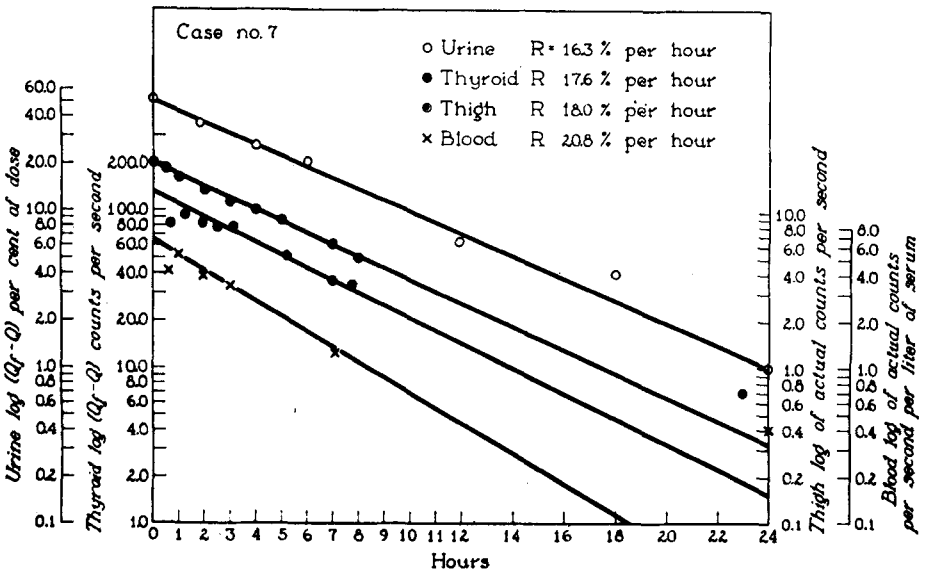


Fig. 1.—Curves of urinary excretion, thyroidal accumulation, radioactivity in the blood, and radioactivity in the thigh plotted on a semilogarithmic scale. The significance of the interrelationship is shown here: it is seen that all four curves have approximately the same rate constant.
From Keating, A. R., and Albert, A. (31).

in Bright's disease, when the kidney is badly damaged, renal secretion may be relatively small. In myxedema, when the thyroid is largely scar tissue, the thyroid clearance will be insignificant. Ordinarily renal and thyroidal clearances together account for the major part of the fate of iodide.

Body Fluids and Other Miscellaneous Tissues—The remainder of the iodide is removed from the blood stream either in body fluids such as saliva and sweat, or by the miscellaneous tissues. For a few hours after the administration of a dose of iodide these miscellaneous functions account for anywhere between 10% and 30% of the administered drug. Ultimately, however, the degradation of metabolic processes turns back this iodide into the blood stream, and it must be lost either through the urine or in other excreta or secretions. A small amount is even lost in the expired air. Although in total amount this "pulmonary clearance" is relatively insignificant, after the administration of therapeutic doses of radio-iodide it amounts to an appreciable radiation. If one holds a Geiger counter under a patient's nose, with each expiration the milliammeter jumps and the monitor crackles. My associate, Dr. Gopal Karandikar, has evidence that this "pulmonary" clearance may be useful in the clinic in judging the concentration of radioactive isotope within the blood stream. For example, in a patient studied by Dr. Karandikar and me, 14 millicuries of radioactive iodine had been administered orally for the treatment of a thyroid cancer. Forty-eight hours after the ingestion of this medication, the total residual I^{131} was estimated at slightly less than 700 microcuries. At this stage the patient exhaled radiation to the extent of almost 2 microcuries per breath while his blood serum ran parallel in specific activity. Like the dragons of old, which in mythical legends breathed forth fire, these modern patients all unwittingly exhale radiation!

THE FATE OF ORGANIC COMPOUNDS CONTAINING IODINE

When one enters into as complex a topic as this, one realizes how much work remains to be done and how difficult it is to generalize concerning the behavior of the multitudinous and varied possible combinations of organic molecules containing iodine. In general, however, as a tentative working hypothesis, it may be possible to discern some properties which seem peculiar to organic compounds of iodine, whereas other properties are attributable chiefly to the particular organic complex involved. Of course some iodine compounds are highly insoluble and in grocery-store dosage would largely be excreted if given orally, or if injected intramuscularly would form solid masses acting locally as foreign bodies. Some of the old-fashioned surgical dusting powders such as thymol-iodide were of this type. It was expected that they would act either through a minimal solubility of a highly active substance or by local decomposition with the release of iodine in some form (such as hyperiodous acid) which might be effective in the immediate vicinity of its origin. Those compounds, like diiodotyrosine, which have a small but appreciable solubility, appear to be distributed fairly uniformly through body fluids with some adsorption on protein molecules. If enough of the material is assimilated, the organic compound ultimately may reach the urine and may even penetrate into serous fluids or into the cerebrospinal fluid. Because decomposition of such a compound inevitably occurs to some extent, however, the investigator must be wary of interpreting the finding of iodine in a certain body fluid or tissue as evidence that the original compound has remained intact. This distinction frequently calls for some rather ingenious microanalytical chemistry in order to distinguish between

the dissolved organic compound in low concentration and iodide itself.

With respect to the blood stream, the presence of these compounds is a constant source of difficulty to the thyroid specialist. This difficulty is of two types. First, the organic compound itself may be associated with the plasma protein and so give a spuriously elevated value for so-called "hormonal" iodine in the blood plasma. Secondly, even more subtle confusion may occur, as pointed out by Salter (34), and by Curtis (28). This is the tendency of iodide (in this case split off from the organic compound) to combine with the plasma protein in the course of time, thus yielding an elevated value for colloidally bound iodine. How to avoid the confusion thus created in clinical diagnosis is one of the important technical problems in practical endocrinology today. The effect is illustrated in Fig. 2, taken from some work

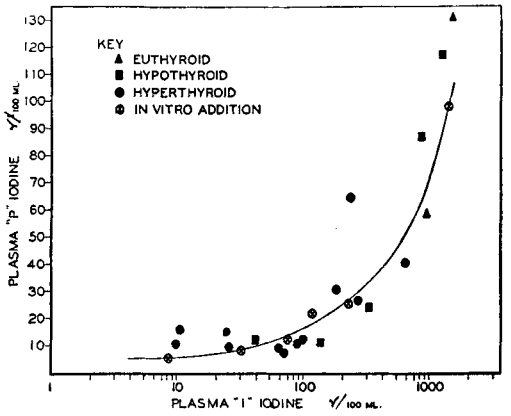


Fig. 2.—A spurious elevation of the protein-bound "P" iodine occurs when the inorganic "I" iodine is unusually high, as described in the text.

From Bassett, A. M., Coons, A. H., and Salter, W. T. (30).

performed in my laboratory nearly ten years ago (30). This false elevation of the protein-bound iodine is found in freshly shed blood. Curtis (28) has shown that a further increase may occur on incubation or standing of the sample in the laboratory. This last effect suggests the presence of an iodase enzyme system in blood, as hypothecated long ago by Blum (27).

One reason why it is important to know well the behavior of these iodine-containing drugs is that they may confuse the hospital chemist who is testing a given patient's blood for an excess of thyroid hormone. Figure 3 shows how well the protein-bound iodine in the blood plasma of man reflects the activity of the thyroid gland. In these 100 cases which I studied in Boston there was an excellent correlation between the analyses for iodine and the diagnosis. The erroneous report of a high organic iodine content might lead to a useless operation involving a border-line decision in diagnosis. Even iodized oil, injected into the spinal canal to delineate a possible tumor, may supply the blood with extra iodine for many weeks. A special chemical treatment is needed to avoid this confusion. Similarly, as shown in Figs. 4 and 5, Dr. Donald Munro and I found that "Skiodan" soon found its way from the spinal fluid into the blood plasma.

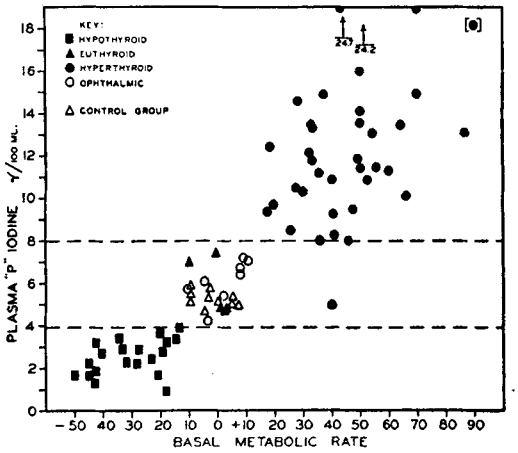


Fig. 3.—In two-thirds of the test cases studied, the clinical diagnosis and the basal metabolic rate were compatible, as shown in the figure. Plasma protein-bound iodine values are given for these cases and for 10 euthyroid controls.

From Salter, W. T., Bassett, A. M., and Sappington, T. S. (34).

An important method of studying such mixtures of natural iodine and pharmaceutical iodine is the use of radioactive iodine. To this end my associate, Dr. Paul Block, Jr., has introduced radio-iodine into certain chemical compounds. For example, radioactive iodide has been introduced into diiodotyrosine and other related phenolic substances by two methods. First by exchange, wherein the phenol-containing compound is allowed to remain in solution with radioactive iodide ions under conditions of temperature and *p*H laid down by Miller, Anderson, Madison, and Salley (36), and by Salter (35). Under these conditions a high proportion of the radioactive iodide enters into the molecule by exchanging with stable iodine already present. Direct iodination has also been employed. In this case the radio-iodide was converted to radio-iodine either by exchange or by oxidation with iodate, and the resulting iodine introduced into the uniodinated molecule by usual synthetic procedures.

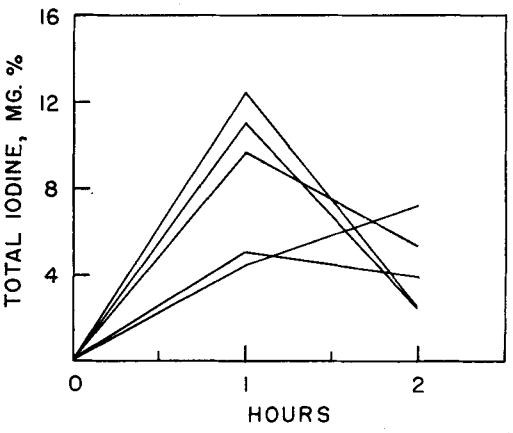


Fig. 4.—Total iodine in human cerebrospinal fluid after intrathecal instillation of sodium salt of mono-iodo-methane sulfonic acid.

From Salter, W. T. (34).

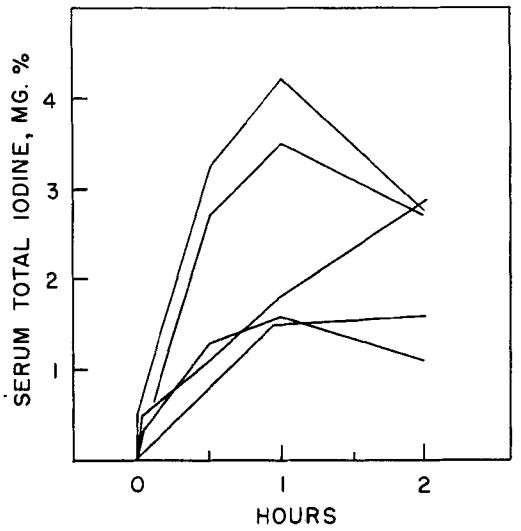


Fig. 5.—Total iodine in human blood serum after intrathecal instillation of sodium salt of monoiodomethane sulfonic acid. Excerpt from data obtained in collaboration with Dr. Donald Munro.
From Salter, W. T. (34).

Radioactive thyroxine has been prepared by direct iodination (37) and by using the exchange method by Frieden, Lipsett, and Winzler (38). Since it would appear that both of these methods would favor the entrance of radioactivity in the phenolic ring of thyroxine rather than in the inner ring, these workers also prepared a sample of thyroxine in which the radioactivity would be expected equally in both rings. They resorted to the expedient of producing radioactive casein, allowing it to undergo the now familiar oxidative process, and hydrolyzing the resultant thyroxine-containing protein.

The Thyroid and Organic Iodine.—At the present time there is *no* evidence that the thyroid can utilize organically bound compounds of iodine. Even in the case of diiodotyrosine, current work indicates that this must first be split into iodide before the thyroid can take it up. Within the gland itself there occurs a complicated sequence of enzymic reactions which can be summarized as follows:

(*a*) An iodinase enzyme system traps iodide within the gland at a differential concentration of several hundredfold, or even several thousandfold, above that of the blood stream. This initial complex can be dissociated readily either by coagulating the protein or by use of an enzymic poison like thiocyanate. Figure 6, taken from work in my laboratory, illustrates this effect.

(*b*) A periodase enzyme system elevates the iodide so trapped to an energy level equivalent to the status of elementary iodine and allows it to combine with diiodotyrosine. This stage can be blocked by some of the common goitrogenic drugs now used in the treatment of thyroid disease, such as thiouracil, propylthiouracil, and certain imidazolines.

(*c*) Two of the resulting diiodotyrosine radicals combine to form thyroxine, i.e., tetraiodothyronine. Whether an organic compound will ever be found which can penetrate the thyroid cells directly and serve as an intermediate in this sequence remains to be learned. It would be interesting in the study of thyroid disease if one could short-circuit the sequence by anticipating one of the synthetic steps in the thyroid's internal economy, but this has not yet been done.

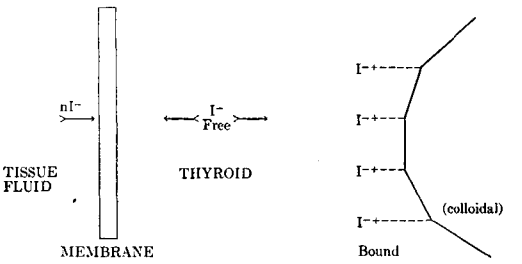


Fig. 6.—From Salter, W. T., Cortell, R. E., and McKay, E. A. (44).

In brief, the thyroid gland seems to depend entirely upon inorganic iodide for its source of iodine wherewith to make thyroxine. The gland is a rugged individualist and prefers to start from the ground up and do all its own synthetic work! In these modern days the availability of radioactive iodide has allowed physicians to take advantage of this fact in two general ways. In the first place, through the use of small test or tracer dosage they have been able to listen to the activity of the thyroid as it picks up iodide, (see Fig. 7). In the second place, by using highly active therapeutic doses, they have been able to trick the thyroid into assimilating miniature beta-ray generators which destroy the gland's parenchyma. The use of this material in certain thyroid cancers is illustrated in Figs. 8 to 12. These specimens of thyroid cancers were removed from the tumors of patients encountered in Connecticut.

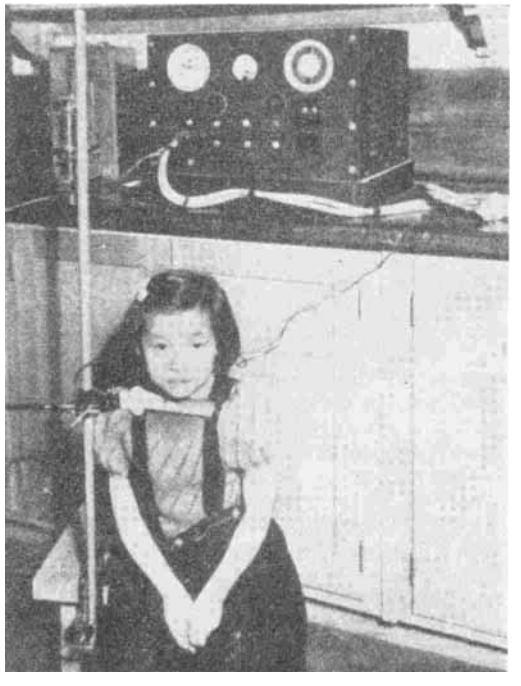


Fig. 7.—From Hamilton, J. G. (42).

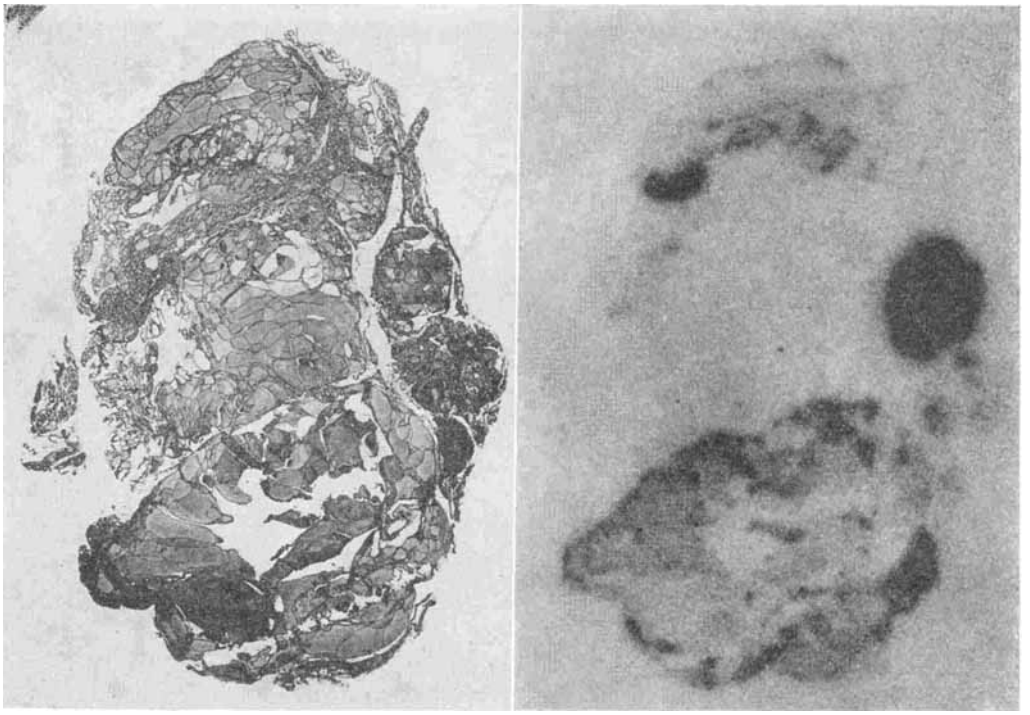


Fig. 8.—Homologous sections of tissue from patient E. S. showing (left) the ordinary histological section stained with hematoxyline-eosin and (right) radio-autograph from the same section.
From Salter, W. T., and Johnston, Mac A. (43).

These figures show how heterogeneous thyroid cancers are, not only among a group of these, but also within a given "lump." These pictures, it will be noticed, are in duplicate. The left-hand version shows the usual stained microscopic section as photographed in daylight. The right-hand version is a "self-portrait" made by each section as it lay on a photographic film in the dark. Because of the radiant energy extruded from these "tagged" specimens, they form a radio-autograph, so-called.

The Liver.—One of the most important features of many compounds of iodine is the role which the liver plays in their metabolism. Whether administered intravenously or absorbed from the intestine by way of the portal circulation, these compounds tend to be trapped in the liver substance. Figures 13

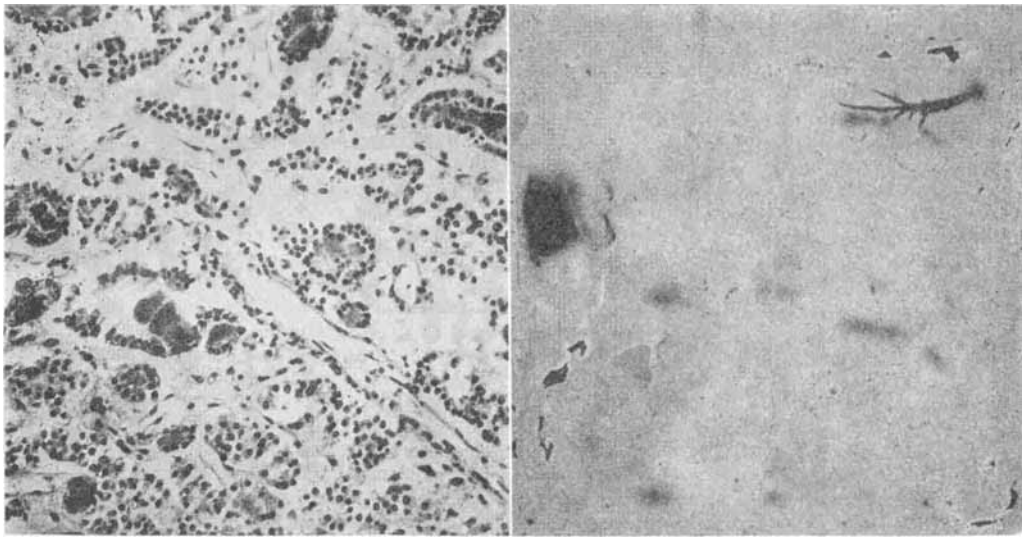


Fig. 9.—Homologous sections from patient N, showing poor fixation of radio-iodide, by a fetal adenoma of the thyroid. On the left is the ordinary histological section stained with hematoxyline-eosin; on the right is the radio-autograph of the same section.
From Salter, W. T., and Johnston, Mac A. (43).

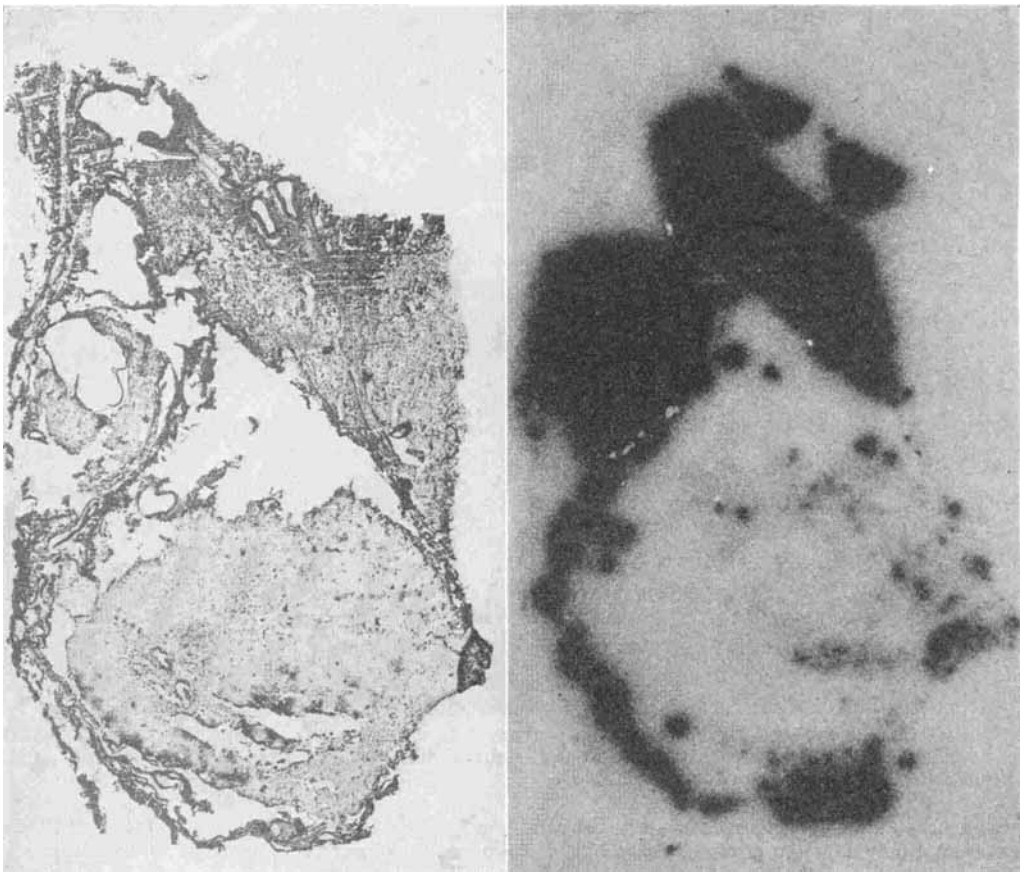


Fig. 10.—Homologous sections of tissue from patient N, showing varying fixation of radio-iodine in different types of tissue, carcinomatous and necrotic.
From Salter, W. T., and Johnston, Mac A. (43).

and 14 illustrate this phenomenon for diiodotyrosine and for "Priodax," respectively. The phenomenon is as if the liver were endeavoring to protect the rest of the body from being invaded by a toxic material. Forthwith, much of this material is poured out in the bile, back into the intestine. Consequently much of the original iodine is eliminated with the feces. To a considerable extent the liver decomposes the compound in the course of its excretion through the bile. In the case of thyroxine, for example, even rather high doses appear in the bile, completely destroyed. As the dose is pushed higher and higher, however, more and more of the original iodine complex appears unchanged. Evarts Graham (23) and his colleagues took advantage of this fact in the development of their "Graham test" for visualization of the gall bladder. The compound commonly used (e.g., tetraiodophenolphthalein) is relatively opaque to X-rays by virtue of its high iodine content, and thus it enables the roentgenologist to visualize the gall bladder. As this material is reexcreted in the bile, of course some of it is absorbed again. Thus a sort of continuous cycle occurs. In the meantime there is constant loss of the material through the intestine and through the kidney. At the same time the drug is undergoing decomposition to a certain extent and iodide is being released.

With all this complex chemical maneuvering going on simultaneously, it is rather difficult to interpret the meaning of a single analysis for total iodine in the blood or urine at any given moment. One must study the whole picture in order to understand the metabolic processes concerned. In particular, one must be prepared to separate organically bound iodine from inorganic iodide which may arise by decomposition. Furthermore, one must be able, if one wishes to do a complete job, to distinguish between the original organic compound and the partial degradation products thereof, in which some iodine still remains attached to carbon, either in the original molecule or in a fragment of it. The chemical formula (V) of Iodophthalein Sodium, U. S. P., also known as "Iodeikon," was formerly used extensively in the X-ray visualization of the gall bladder.

Renal Excretion.—In addition to iodide which results from decomposition, in the case of certain compounds there is often a considerable renal excretion of organically bound iodine. The extent to which this occurs is partly dependent upon the ease of decomposition of the organic molecule. A considerable number of organic molecules are known which are excreted in large measure by the kidney. Some of these, as originally described by Mosenthal (39), may be used simultaneously as a test of liver

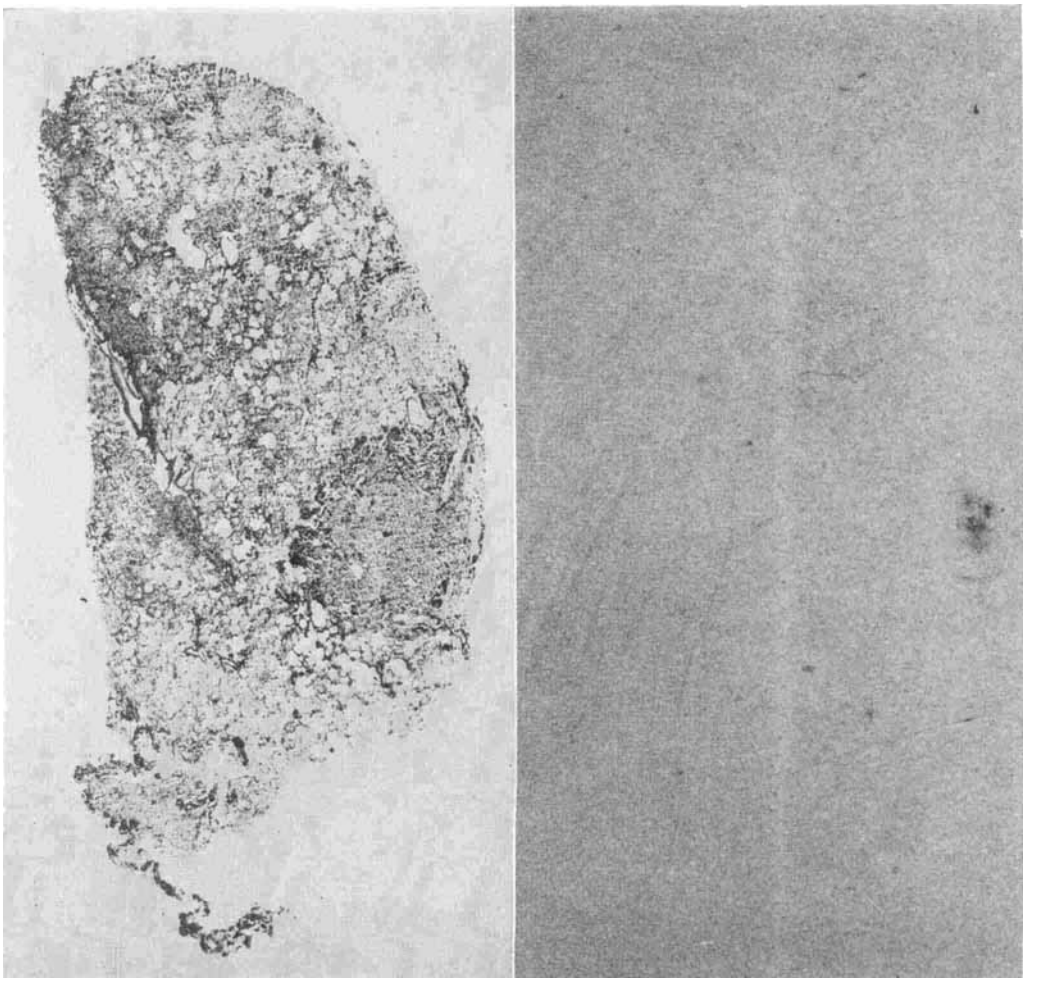
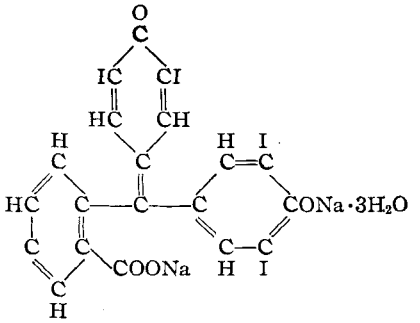


Fig. 11.—Homologous sections of tissue from patient V showing (left) lung metastasis, (right) radio-autograph of the same. Note that several months earlier this metastasis failed to fix radio-iodide and that later the fixation (although poor) became definite.
From Salter, W. T., and Johnston, Mac A. (43).



Iodophthalein Sodium
(V)

and of renal function. The more modern compounds, however, have been developed primarily for use in the urinary tract. Not only are they used in the clinic to visualize the urinary passages, but they are used by physiologists to test kidney function. As described by Homer Smith (25) and others, they constitute a convenient means of studying the activity and the mass of tubular tissue because they are excreted in large measure by tubular secretion. Table I, taken from Smith and Ranges (25), describes the properties of five such compounds. These are "Diodrast," "Hippuran," "Iopax," "Neoiopax," "Skiodan." As will be described presently, another compound known as "Priodax" has similar properties.

RELATION OF CHEMICAL STRUCTURE TO METABOLIC FATE

In the present state of our knowledge it is very difficult to compare various iodine compounds with respect to their stability in the organism. Compounds as widely differing as ethyl iodide, thyroxine, and tetraiodophenolphthalein are used in medicine regularly. They all yield a certain amount of inorganic iodide in the animal organism. In the case of thyroxine, to my knowledge, no one has ever isolated intact thyroxine from the urine, but the

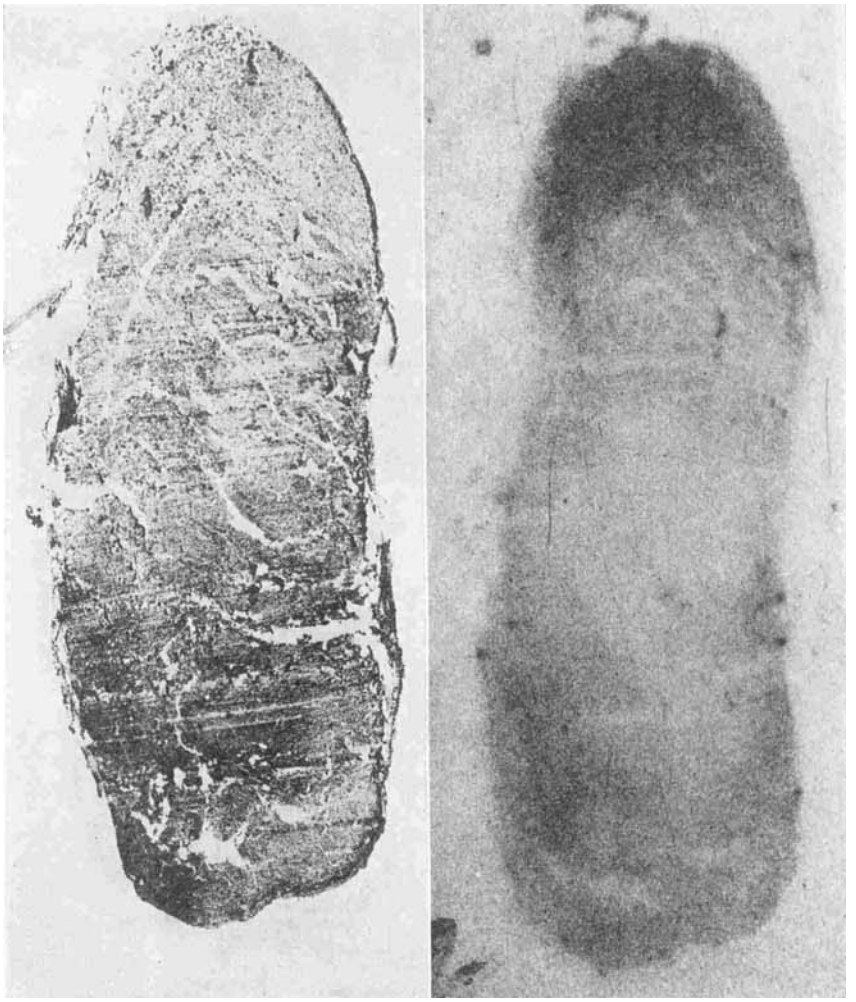


Fig. 12.—Homologous sections from hilar nodes from patient V showing (left) ordinary histological section and (right) radio-autograph of the same.
From Salter, W. T., and Johnston, Mac A. (43).

drug is so powerful that even stout men can endure only a relatively few milligrams at a time. Its decomposition product or precursor, diiodotyrosine, likewise is readily decomposed. Because it is less active pharmacologically, larger doses may be given up to the point that the unaltered organic substance can be found in the urine as well as in the blood stream. Even so, a considerable portion of it is split into inorganic iodide.

The amounts of Iopax, i.e., "uroselectan," and of tetraiodophenolphthalein which are given for X-ray visualization are very large in comparison with the ordinary metabolic consumption of thyroxine or diiodotyrosine. Consequently, it is not surprising that a considerable proportion of these materials is excreted unchanged. This finding does not necessarily mean, however, that these materials are less susceptible to decomposition in the body. It means simply that bodily mechanisms which ordinarily would decompose these compounds have been overwhelmed temporarily. It will be desirable to make a careful study of the fate of widely differing types of organic chemical compound at the same level of molecular concentration in body fluids and in molecular-equivalent doses. Such a study ultimately will disclose many interesting features about the stability of different types of iodine linkage in varied organic structures. It will also disclose preferential excretion or concentration in the several organs of the body.

At the moment an investigation of this sort is in progress in the Laboratories of Pharmacology and Toxicology at Yale. For instance, a series of compounds, largely contributed through the courtesy of Dr. Henderson of Schering Corporation, is under investigation. These substances are derived theoretically from diiodotyrosine by substitution of various inherent constituent groups. Into these molecules not only stable but radio-iodine has been incorporated so that the tracer technique can be used as well as routine analytical methods. Among these compounds are included the following: Cyclohexyl diiodohydroxyphenyl propionic acid (VI); Phenyl diiodohydroxy cinnamic acid (VII); and the ethyl ester of phenyl diiodohydroxyphenyl propionic acid (VIII).

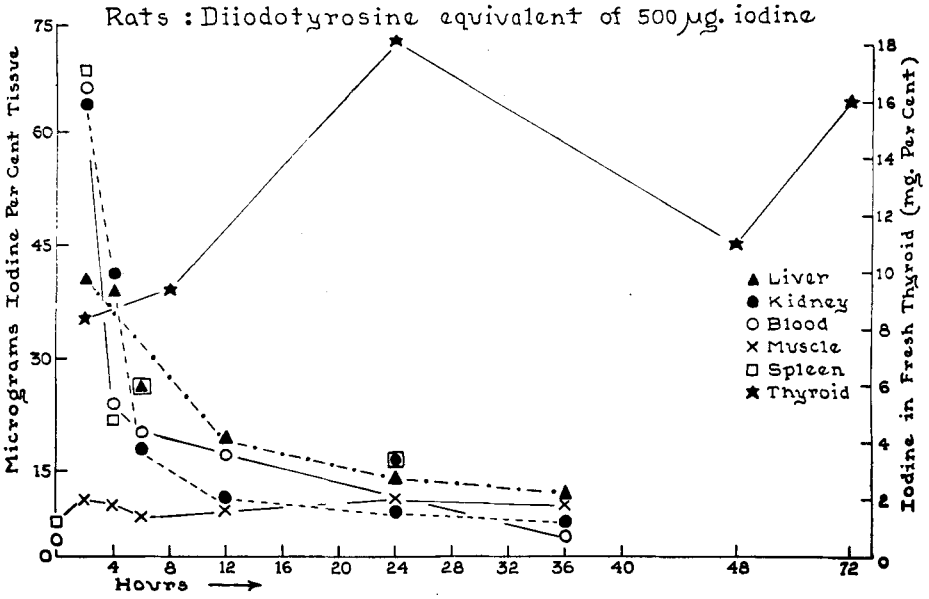
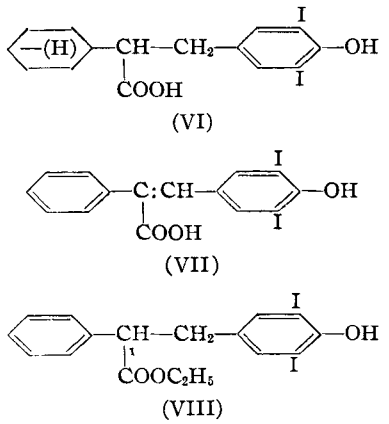
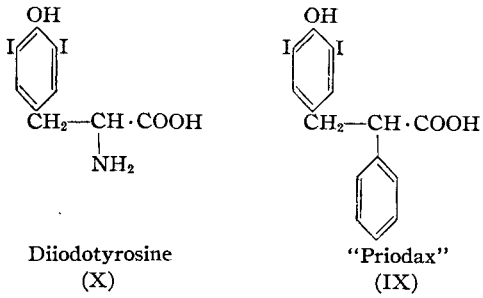


Fig. 13.—The iodine distribution in various rat tissues is shown after the intraperitoneal injection of "500 micrograms iodine as diiodotyrosine" at various intervals of time. The thyroid value is charted in milligrams per cent on the right ordinate; values for the rest of the tissues in micrograms per cent on the left ordinate. The kidney and blood serum show higher initial contents than does the liver. After such high doses the protein-bound iodine rises more than does the iodide fraction. With smaller doses the reverse is true.



Their metabolic fate is being contrasted with that of the mother or prototype substance, diiodotyrosine. Figures 13 and 14 illustrate the behavior of "Priodax" [β-(4-hydroxy-3,5-diiodophenyl)-α-phenyl propionic acid] as compared with diiodotyrosine when both are injected into litter-mate rats intraperitoneally at the same molecular dosage (40). The concentration of the "Priodax" in the liver at the end of three hours is of special significance. The fact, however, that some concentration also occurs in the kidney tissue indicates that this substance, like the "uroselectan" ("Iopax") or "skiodan" group of materials, may also be used to study renal function (41).

It will be observed below that this "Priodax" (IX) is a drug made (on paper, at least) from the natural metabolite *diiodotyrosine* (X) by substituting a phenyl group for an amino group.



A chief result of this substitution is a predilection for the biliary route of excretion, whether the material be administered orally or by intravenous injection. Like its natural relative diiodotyrosine, however, it still preserves a trend toward renal excretion as well. This is shown by the experimental results already given in Figs. 13 and 14.

Some of these derivatives of diiodotyrosine also share the properties of other organic iodine compounds previously mentioned. For instance, phenyl diiodohydroxy cinnamic acid has interesting properties as a remedy against the organism which causes amebic dysentery. In this respect it recalls the effect of "Chiniofon," which has already been discussed. Likewise, cyclohexyl diiodohydroxyphenyl propionic acid shows bactericidal action against Shigella dysentery organisms in cultures, at least. In general, therefore, this group of chemical congeners illustrates how drugs of different actions may be formed by altering the chemical constitution of a single parent molecule. Obviously such derivatives will retain many of the metabolic peculiarities of the parent substance.

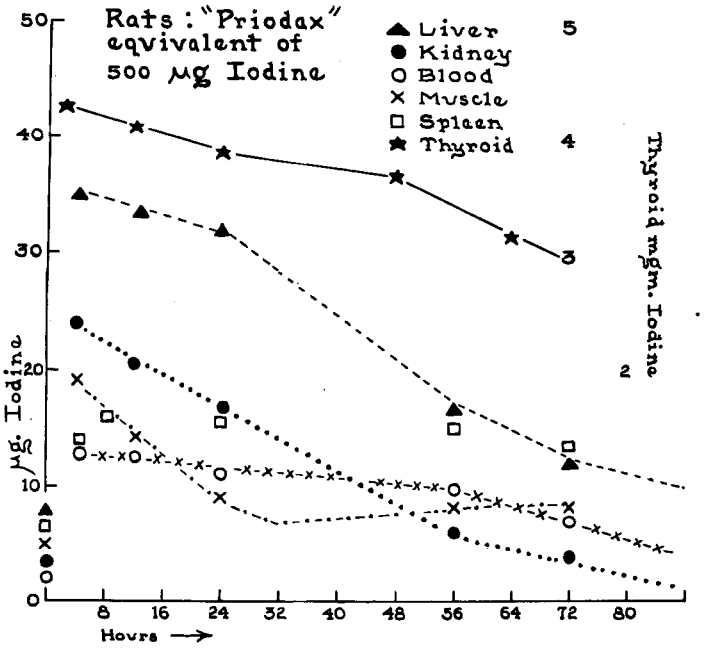


Fig. 14.—For comparison with the data on diiodotyrosine given in Fig. 13, this graph shows the relative distribution of iodine in micrograms iodine as "Priodax," administered I.P. The tissue concentrations are given on the left ordinate; those for the thyroid on the right ordinate. On such high doses the compound raises the "protein-bound" fraction of iodine more than the "iodide" fraction in tissues. In smaller doses it is the iodide fraction which rises higher. Note that in Fig. 13, the thyroidal iodine concentration is adjusted for a hypothetical 100 Gm. of rat. In Fig. 14, the iodine is that per 10 Gm. of wet thyroid, as found in the 300-Gm. rats studied.

DISCUSSION

Thus far we have spoken largely of the empirical fate of certain iodine-containing complexes and their particular predilection for certain organs or parasites. We have also mentioned the possibility that some are more susceptible to destruction by protoplasmic enzyme systems than are others, and that this fact may be used either negatively or positively for therapeutic purposes. There is one further aspect of the incorporation of iodine into organic compounds which has been very little explored as yet. This is the development of molecular competitors which may serve as blocking agents in normal metabolic processes. This underhanded trick also may be played against the bacterial or plasmodial cell. Indeed it has long been a puzzle why some of our best antimalarial drugs contain halogen, i.e., chlorine, in the molecule. Doubtless there will be found other parasiticides and perhaps antibacterial agents in which an iodinated molecule is highly effective. Already iodine has appeared in such compounds as "Vioform," so effective against pseudomonas or lamblia-like organisms.

We noted at the start that the most important iodine-containing drugs *used for internal action* could be classified arbitrarily as (*a*) thyroid drugs and (*b*) nonthyroidal. We must now add the reservation that some drugs appear to straddle this distinction. Diiodotyrosine plays an important role in the internal economy of the thyroid gland and in the chemist's synthesis of thyroxine. When simple substitutions are made in its constituent chemical radicals, however, it becomes a diagnostic aid in liver problems or even a remedy for amebiasis.

Moreover, the parent molecule diiodotyrosine is formed whenever tincture of iodine meets blood or flesh or bacterial protoplasm. Thus step by step, the pharmaceutical chemist and the pharmacologist watch the gradual evolution of new drugs by simple but progressive changes in well-known molecules. As in the parlor game, played by young ladies at house parties with folded paper, they are often astonished at the final result produced by random additions to the original picture!

SUMMARY

In summary, then, the metabolism of iodine-containing drugs within the body resolves itself first of all into the history of inorganic iodine and of organic iodine. Whenever an organic compound is administered to a mammal, varying amounts of iodide are liberated by decomposition, so that one is never rid of the question of *inorganic* metabolism. Our most potent drugs, e.g., thyroxine, are so completely decomposed that their final degradation products as thus far detected have consisted entirely of the iodide ion alone.

With regard to the fate of organic iodine compounds, at the moment they can be divided into two great classes, i.e., first, those connected with the internal economy of the thyroid; and secondly, those which are more strictly pharmaceutical in nature. In the first group, in addition to

iodide, the chief compounds to be considered are diiodotyrosine and thyroxine, together with some of their simpler derivatives. In the latter group a great variety of compounds is possible. Apart from local or parasiticidal action, however, thus far most of them are distinguished by their concentration in the liver and in the kidney. In connection with their hepatic concentration they serve a useful purpose in visualizing the gall bladder and biliary passages by virtue of the high radio-opacity of the constituent iodine atoms. The same radio-opaque effect is also applicable to the urinary passages, but in addition such iodine-containing materials may be used to measure tubular function or tubular mass. This same radio-opaque effect has also been used in other situations, notably in the spinal canal where the detection of tumor masses or of blockage is important.

Because the persistence of these molecules in intact form is a matter of considerable importance if their pharmaceutical action is to be preserved, careful studies of the types of compound which are least liable to immediate disintegration within the organism are indicated. Similarly more careful and extended studies are needed of the effect of introducing iodine into some of the better known drugs, in order to ascertain whether their potency or their specificity can thereby be enhanced.

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WHO MAKES IT?

The National Registry of Rare Chemicals, Armour Research Foundation, 33rd, Federal and Dearborn Streets, Chicago, Ill., seeks information on sources of supply for the following chemicals:

Sphaerophorin
Atraric acid
Divarin
Pulvinic acid and methyl ester
L-α-Glycerylphosphorylcholine
d-Laudanosine
Canadine
Barbatinic acid
4-Amino-8-nitroquinoline
Obtusatic acid
Divaricatic acid
Atranorin
Shikimic acid
2,3-Dimercaptopropyl ethyl ether
2-Methyl-8-hydroxyquinoline
Muscarine
Bulbocapnine
Adenine thiomethyl pentoside
Phosphorylthiocholine
L-Mannose