

ORGANIC IODIN PREPARATIONS, THEIR PHARMACOLOGY AND THERAPEUTIC VALUE *

FRANKLIN C. McLEAN, M.D.

PORTLAND, ORE.

The introduction within recent years of numerous organic iodine compounds as substitutes for the iodides, the extravagant claims made for some of them by the manufacturers, both as regards therapeutic efficiency and absence of toxic side actions, and the scarcity of literature on the subject in American periodicals seem to demand a review of the entire subject of the value of these substances as therapeutic agents. Most of these compounds have originated from German manufacturers, and nearly all of the investigations regarding them have been published in that country. These substances, however, are being rapidly introduced into the American market, and at the suggestion of the Council on Pharmacy and Chemistry of the American Medical Association, I have undertaken an investigation of the pharmacological basis for the use of such compounds as substitutes for the iodides. The present paper deals chiefly with the literature on the subject.

I.—CLASSIFICATION AND CHEMICAL NATURE

Most of the organic iodine preparations introduced up to the present time as substitutes for inorganic iodides are addition products of iodine with either proteins or unsaturated fatty acids or fats. Other organic combinations of iodine have usually so great an action due to the remainder of the molecule that the iodine action is obscured, and they are as a rule not suitable for administration as substitutes for the iodides.

A. *Iodized Albumins or Proteins*.—The first iodized albumins were prepared by Boehm and Berg.¹ The resulting product could be easily deprived of its iodine by washing with water, or by dialysis, so that the combination between the iodine and the albumin was not firm, and they considered that the iodine was mechanically held. Liebrecht and Roehmann² iodized casein by warming it with iodine. The resultant compound contained no free iodine, but gave off iodine on washing with water and alkalis. Their "Periodcasein" held 17.8 per cent. of iodine, but after washing it left "Iodcasein" with 5.7 per cent. Both compounds split off sulphur and phosphorus easily. Hofmeister³ prepared iodo-albumin from

*From the laboratory of biochemistry and pharmacology, University of Chicago.

*Submitted for publication Sept. 17, 1912.

*Investigation supported by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

1. Boehm and Berg: Arch. f. exper. path., 1876, v, 329.

2. Liebrecht and Roehmann: Arch. f. exper. Path., 1894, xxx, 1824.

3. Hofmeister: Ztschr. f. physiol. Chem., 1897, xxiv, 159.

crystallized egg albumin. Many other iodized proteins are now on the market, and several of them are described below. Most of these preparations no longer give the Millon reaction, and on this account it has been considered that the tyrosin group in the protein molecule has taken up the iodine. To bear this out, a tyrosin-iodine compound (3-5 diiodotyrosin, an iodine complex found in sponges⁴ and other places in nature) has been separated from a number of the iodized proteins by hydrolysis (*vide infra*). Undoubtedly, however, as shown by Oswald⁵ and by Pauly,⁶ other groups in the protein molecule are also involved in the combination, and according to their work it is probable that both histidin and phenylalanin may take up iodine when a protein is iodized. It has been shown that many of the commercial preparations of iodized proteins consist of a mixture of a true compound of iodine with the protein molecule, of inorganic iodide, possibly loosely combined, and in some cases, of free iodine. The nature of the commercial preparations of iodized proteins so far studied may be here briefly summarized. Many of these preparations are not yet on the American market.

COMMERCIAL PREPARATIONS

Iodalbacid (Fabrikanten Herrn Gans in Frankfurt) is a commercial iodized albumin, said to be obtained by electrolyzing an iodide solution in which the anode is surrounded by a protein. It is said to contain 10 per cent. of iodine. Oswald⁷ hydrolyzed this compound and obtained 0.4 gram of diiodotyrosin from 100 grams original substance. Taege⁸ also examined this substance and found it to contain only 5.5 to 5.6 per cent. of iodine. He found it free of inorganic iodine, and found no iodine split off on shaking with water, and concluded that all the iodine is bound in the molecule. When given by mouth he found that 66 per cent. of the iodine was excreted in the urine within eighty hours, 60 per cent. in organic combination and 6 per cent. in inorganic form.

Iodized egg white is manufactured in three forms (Chem. Fabrik von Dieterich in Helfenberg): (1) *Iodeigon* is an iodized, water insoluble, egg albumin, with 20 per cent. of iodine. This compound was studied by Taege,⁸ who found that 95 per cent. of the total iodine was in loosely combined, inorganic form, mainly as hydriodic acid, and this was easily split off on shaking with cold water. On giving this compound by mouth he found that the excretion ended in ninety hours, with the excretion of 76.4 per cent. of the total iodine, with 23.4 per cent. in organic form and 53.0 per cent. in inorganic form. (2). *Iodeigonatrium* is a

-
4. Wheeler and Mendel: Jour. Biol. Chem., 1909, vii, 1.
 5. Oswald: Ztschr. f. physiol. Chem., 1909, lviii, 299.
 6. Pauly: Ztschr. f. physiol. Chem., xliii, 2243.
 7. Oswald: Ztschr. f. physiol. Chem., 1911, lxx, 311.
 8. Taege: Med. Klin., 1910, vi, 1536.

water soluble, sodium salt of an iodized egg albumin, said to contain 15 per cent. of iodine. This compound was examined by Oswald,⁹ who found 96 per cent. of the iodine split off after four and one-half hours' boiling with saturated barium hydrate. He was unable to separate iodotyrosin from this substance. Mosse and Neuberg¹⁰ also examined this compound and found only a little iodine split off on boiling with dilute acids. (3) *Peptoidragon* (iodopeptone), a third form, contains 15 per cent. of iodine. *Iodomangan*, N. N. R., contains 1 per cent. of this compound.

Iodglidin (Klopfer, in Dresden) is an iodized plant albumin (gliadin) containing 10 per cent. of iodine, of which 38.4 per cent. is in loosely combined, inorganic form (Taage). Taage gave this compound by mouth and found 63.2 per cent. of the iodine excreted in seventy-eight hours, with 48.2 per cent. in inorganic form and 15 per cent. in organic combination. Neuberg¹¹ hydrolyzed this compound with 30 per cent. sulphuric acid at 40 C., and separated a crystalline copper salt containing 52.25 per cent. iodine, but he did not obtain diiodotyrosin. Oswald⁷ also hydrolyzed iodoglidin and obtained 7.3 per cent. of the original iodine present as diiodotyrosin, using saturated barium hydrate as the hydrolyzing agent. Wheeler and Mendel¹² also found diiodotyrosin on hydrolysis. According to Broking,¹³ iodglidin is very unstable, affected by light, pepsin, trypsin, etc. The iodine is firmly combined only in part, and a much greater part is loosely held, this agreeing with the results of Taage. Boruttau¹⁴ showed that iodine could be split off by digestion with pepsin, treating with alcohol, or boiling with acids.

Iodalbin, N. N. R. (Parke, Davis & Co.), is said to be a compound of iodine with blood albumin, containing approximately 21.5 per cent. of iodine. It is said to contain no free iodine, unless decomposed. It is insoluble in the ordinary solvents, but soluble in alkalis. I have examined samples of this substance, obtained in the open market, and find the claims as to the total amount of iodine to be substantiated, as I have found 21.6 per cent. of iodine. The dry substance gives a strong blue color with starch paste. On shaking for a few minutes with a dilute solution of potassium iodide (6 gm. in 500 c.c.) an amount of iodine equivalent to 3.1 per cent. of the original weight of the substance is separated from it. On shaking for four hours in distilled water, at room temperature, I have found an amount of iodine equivalent to 4.9 per cent. of the original weight of the substance to be separated off. The considerable amount of

-
9. Oswald: *Ztschr. f. physiol. Chem.*, 1911, lxxii, 374.
 10. Mosse and Neuberg: *Ztschr. f. physiol. Chem.*, 1902-3, xxxvii, 427.
 11. Neuberg: *Biochem. Ztschr.*, xxvii, 251.
 12. Wheeler and Mendel: *Biochem. Ztschr.*, 1910, xxix, 419.
 13. Broking: *Ztschr. f. exper. Path.*, 1910, viii, 125.
 14. Boruttau: *Deutsch. med. Wchnschr.*, 1907, 1490.

free iodine which the substance contains would doubtless prove irritating in the stomach.

Iodomenin (Herr Wölfig, Berlin) is a compound of albumin with the bismuth iodine. It contains 4.45 per cent. of iodine (Taege⁸), and of this 94.4 per cent. is split off by shaking with water, most of it being united to bismuth. Taege gave this substance by mouth, and found 81.4 per cent. of the total iodine given, excreted in ninety hours, 65.7 per cent. inorganic, and 15.7 per cent. inorganic combination.

Proiodin (Wolf, in Bielefeld) is an iodized casein with an iodine content of 4.23 per cent. (Taege⁸), that is firmly bound in the protein molecule. Practically all of this substance is excreted in organic combination.

Iodomaisine is the iodized product of the albumin from corn meal (zein) containing 44.68 per cent. of iodine. It gives both the biuret and Millon reactions.

Iodtropin (Troponwerken in Mülheim) contains 5 per cent. of iodine. Of the total iodine only 3.37 per cent. is split off on shaking with cold water, leaving 96.63 per cent. in organic combination. In sixty hours only 13.2 per cent. of total iodine given was found in the urine (Taege⁸), and at that time the urine was free of iodine.

B. *Iodized Fats and Fatty Acids*.—The first iodized fat to be recommended for therapeutic use was described by Winternitz.¹⁵ It was introduced into the market under the name of Iodipin (*vide infra*). Since then numerous other compounds have been manufactured, their composition depending on the fact that the free valences in unsaturated fatty acids may be satisfied by iodine. The resulting compounds are generally free from free iodine, and do not yield their iodine readily, except on hydrolysis. They are generally, therefore, more stable than the iodized albumins.

Iodipin, N. N. R. (Merck), is the product of the addition of iodine chloride to oil of sesame. It is on the market in two forms, one of 10 per cent. strength, and the other of 25 per cent. strength, for hypodermic use. The darker color of the 25 per cent. preparation is not due to free iodine, but to a resin-like body which the oil contains.¹⁶

Sajodin, N. N. R. (Farbenfabriken von Elberfeld), is the calcium soap of a fatty acid obtained by iodizing erucic acid, forming iodo-behenic acid. The formula is said to be $(C_{21}H_{42}IOO)_2Ca$. Theoretically this should contain 26.03 per cent. of iodine. Two samples analyzed by me showed an iodine content of 22.46 per cent. and 22.58 per cent. On boiling for fifteen minutes with 25 per cent. sulphuric acid, the substance splits off the iodized fatty acid, which by further hydrolysis yields its iodine.

15. Winternitz: Deutsch. med. Wchnschr., 1897, xxiii, 477.

16. Winternitz: München. med. Wchnschr., 1903 I, 1241.

Lipoidin is a new iodized fatty acid ester described by Loeb and van der Velden.¹⁷ It is the ethyl ester of a diiodized, unsaturated fatty acid of the formula $C_{24}H_{44}I_2O_2$, containing 41.06 per cent. of iodine. It is soluble in 70 per cent. alcohol, also in oils, fats, benzol, chloroform, and insoluble in water.

Iodostarin (Hoffmann-La Roche Chemical Works) is a new diiodized fatty acid of the formula $C_{18}H_{32}I_2O_2$, and should contain 47.5 per cent. of iodine. The Hoffmann-La Roche company has furnished me with sample tablets of the substance, each containing 0.25 grams of the compound, and said to contain 0.12 grams of iodine. In my analysis of these tablets I have found the iodine content to be 46.53 per cent., each tablet containing 0.116 grams. Iodostarin occurs as a colorless powder, insoluble in water, but soluble in alcohol, ether, etc.

Iodival (Knoll & Co.) is iodoisovalerianyl urea, corresponding to the bromide compound "Bromural," N. N. R. It is somewhat soluble in water. It is said to contain 47 per cent. of iodine.

C. *Other Organic Iodin Compounds.*—The other organic iodine compounds used therapeutically are used mainly for their antiseptic action. Iodoform (CHI_3) has, of course, priority over the rest of these. Numerous substitutes for iodoform have been introduced, such as *Thymol Iodid*, U. S. P. (Aristol); *Europhen*, N. N. R.; *Airol*, N. N. R.; *Iodone*, N. N. R.; *Iodoformogen*, N. N. R.; *Vioform*, N. N. R., etc. If these substances are given internally they are split in the body, and the iodine is liberated in the form of iodides, and excreted, but the substances themselves and their decomposition products in the body have certain toxic actions (such as that of iodoform) which render them unsuited for internal use.

Iothin, N. N. R. (Farbenfabriken von Elberfeld Co.), is di-iodo-hydroxy-propane, obtained by chlorinating glycerin and replacing the chlorine by iodine. It is a yellowish, oily, heavy liquid, said to contain 77 per cent. of iodine, and is recommended for application to the skin in the form of inunctions, for absorption.

Glycerodin, N. N. R. (H. K. Wampole), the glycerite of hydriodic acid, is not a true organic preparation.

Iodocitin is a recently described compound of iodine and lecithin.¹⁸

II.—ABSORPTION AND EXCRETION

Since most of the organic iodine preparations used internally are addition products of iodine with proteins or fatty acids, the question of their absorption is intimately concerned with the physiology of the

17. Loeb and Van der Velden: *Therap. Monatsh.*, 1911, xxv, 209.

18. Neuberg: *Therap. d. Gegenw.*, August, 1911.

absorption of the proteins and fats. As certain changes occur in these substances in the process of digestion and absorption, we expect to find that their iodine addition products will undergo certain similar changes in the gastro-intestinal tract. Boruttan¹⁹ has carried on artificial peptic and pancreatic digestion of the iodized proteins, and has determined the amount of iodine present in the splitting products obtained. He found that the compounds which are easily deprived of their iodine by washing, etc. (such as iodoglycin), yield it readily on digestion, and a relatively large amount appears as inorganic iodide, while a relatively small amount remains in the undigested residue. The reverse is true of the more stable compounds, such as iodalbumin. He found iodine in all the fractions of acid proteins, peptones, etc. He concluded that the splitting off of inorganic iodine did not occur in the stomach, though it could be produced outside the body by peptic digestion, but that the splitting products of the proteins left the stomach before that stage had been reached, and that the process was completed by pancreatic digestion, and that a large amount of the iodine was absorbed in the form of inorganic iodides. V. Fürth and Friedman²⁰ demonstrated that when iodalbumin, one of the more stable compounds, was fed, most of the iodine was carried in the blood in inorganic form. Some absorption of the iodine in the form of iodized splitting products of the proteins also occurs, the amount depending on the amount of iodine which is firmly bound in the protein molecule. As 3-5 diiodotyrosine has been obtained from hydrolysis of many of the iodized proteins, it is probable that a part of the iodine is absorbed in that form, and similar forms. Mosse and Neuberg²¹ found iodhippuric acid in the urine on feeding iodoacetate to rabbits, and found iodbenzoic acid in the blood on feeding the same substance to dogs. Oswald²² was unable to confirm their results, and concludes that the iodine in the preparation used was not held as diiodotyrosine.

The form in which the iodine, fed in the form of iodized proteins, is excreted depends largely on the form in which it is absorbed. Taege⁸ has shown a close parallelism to exist between the stability of the iodized proteins and the amount of organic iodine in the urine. It is probable, therefore, that a large part of the iodine absorbed in organic combination is excreted in practically the same form, without ever being liberated in inorganic form. This is borne out by the work of Oswald,²³ who fed 3-5 diiodotyrosine to rabbits, and found that about half of the iodine given was

19. Boruttan: *Ztschr. f. exper. Path. u. Therap.*, 1910, viii, 418.

20. Von Fürth and Friedman: *Arch. f. exper. Path., Festschr. f. Schmiedeberg*, 1908, p. 214.

21. Mosse and Neuberg: *Ztschr. f. physiol. Chem.*, 1903, xxxvii, 419.

22. Oswald: *Ztschr. f. physiol. Chem.*, 1910, lxxv, 141.

23. Oswald: *Ztschr. f. physiol. Chem.*, 1909, lxxii, 399.

excreted in the urine in organic combination, partly in the same form in which it was given. This iodine would necessarily, therefore, be devoid of any iodine "ion action." Abderhalden and Slavu²⁴ gave 3-5 diiodotyrosine by mouth and subcutaneously and found most of the iodine in the urine in inorganic form. They found some in organic combination, but not as diiodotyrosine. They found, however, a considerable amount of diiodotyrosine in the feces, even when the substance was given subcutaneously.

The fate of the iodized fats is similar to that of the fats and fatty acids themselves. They generally pass through the stomach unchanged²⁵ and are split in the intestines and absorbed. In the case of sajodine, the calcium is probably first split off, as this change occurs first on hydrolysis, and following this there is at least partial splitting off of the iodine from fatty acid. Metzger²⁶ fed sajodine to dogs with intestinal fistulae, and showed the presence of inorganic iodine in the duodenum during digestion. With iodipin he was unable to demonstrate any inorganic iodine in the stomach or upper duodenum. According to Winternitz,¹⁶ iodipin is not absorbed in the stomach, but is split in the intestines by the bile and pancreatic and intestinal juices, leaving the iodine bound to the fatty acid, and is absorbed mainly as the iodized fatty acid. He showed that the iodine was present in the ether extract of the blood after absorption, and concluded that it was identified with the fats there. By oxidation of the iodized fatty acid in the blood and in the tissues the iodine is split off in the form of iodide and excreted. Wells²⁷ concluded that when iodipin was injected subcutaneously it was carried in the blood mainly as inorganic iodine. Boruttau¹⁹ gave sajodine and iodival in large doses to dogs, took blood from the carotid, and found that much more iodine was present in the blood in inorganic than in organic form. Abderhalden and Kautzsch²⁸ concluded that sajodine was absorbed as the mono-iodobehenic acid, and was taken into the cells in that form, and that iodine was liberated by oxidation in the cells. My analysis of the liver after giving sajodine (*vide infra*) would indicate that a part of the iodine is present in the tissues as the iodized fatty acids, though I do not regard this as sufficiently demonstrated.

Loeb and van der Velden¹⁷ showed that iodival is absorbed without any inorganic iodine being split off in the intestine. Broking¹³ came to the same conclusion.

24. Abderhalden and Slavu: *Ztschr. f. physiol. Chem.*, 1909, lxi, 405.

25. Posternak, *Bull. Soc. de therap.*, series 4, 1910, xi; *Bachem: München. med. Wehnschr.*, 1911, No. 41.

26. Metzger: *Med. Klin.*, 1911, vii, 1390.

27. Wells: *Ztschr. f. physiol. Chem.*, 1905, xlv, 412.

28. Abderhalden and Kautzsch: *Ztschr. f. exper. Path. u. Therap.*, 1907, iv, 1.

When the iodized fats are taken the greatest amount of iodine leaves the body in the urine in the form of potassium iodide,²⁹ though a small amount is present in the urine in organic combination. This is of no significance, as about 9.9 per cent. of iodine given as potassium iodide may appear in the urine in organic combination (Taegge⁸), and Harnack³⁰ has shown that a spontaneous change from iodide to organically combined iodine may occur under normal circumstances in fresh urine.

The excretion of iodine in the milk, when given in the form of iodized fats, is of interest. Löns³¹ fed lipoiodine and found greater amounts of iodine in the milk than when corresponding amounts of potassium iodide were fed. He was unable, however, to identify the iodine in the milk with the milk fat. Winternitz¹⁵ fed iodized hog fat to a goat, and found iodine in the milk in the form of an iodized milk-fat, and also in the milk serum in inorganic form. In seven days 6.2 per cent. of iodine given was excreted in the form of iodized milk-fat.

The absorption of iodine compounds from other places than the gastrointestinal tract has been studied. The absorption of iodipin when administered subcutaneously has already been mentioned. Winternitz¹⁶ showed that iodipin was not absorbed through the unbroken skin, as the urine remained iodine-free, and he also showed that not over 10 per cent. was absorbed when administered by rectum. Iothion, which is of the nature of an iodized volatile oil, is rapidly absorbed through the unbroken skin,³² appearing in the urine in about one hour. It is irritant to the skin, and is usually applied in the form of an inunction, using lanolin as a base.

RATE OF ABSORPTION AND EXCRETION

The rate of absorption and excretion of the organic iodine preparations has been studied mainly in comparison with the excretion of potassium iodide. The excretion of potassium iodide has been studied by many observers, and the results agree in general with those of Anten,³³ who showed that (1) after one dose of potassium iodide (0.5 grams) the highest amount in the urine is in the second hour, rarely in the first or third; (2) the average amount excreted in the urine after this dose is 75 per cent. (minimum, 65 per cent., maximum, 85 per cent.); (3) the duration of the presence of iodine in the urine after such a dose of 0.5 grams is forty hours. After two doses five hours apart the duration is fifty-six hours, and after three doses in ten hours is seventy-seven hours; (4) when mucilaginous bodies are given with potassium iodide the excre-

29. v. Klingmüller: Berl. klin. Wehnschr., 1899, p. 540; Winternitz: München. med. Wehnschr., 1903, 1, 1241.

30. Harnack: Arch. internat. d. Pharm. u. Therap., 1910, xx, 247.

31. Löns: Berl. klin. Wehnschr., 1911, xlviii, 2064.

32. Kellermann: Ztschr. f. exper. Path., 1905, ii, 416.

33. Anten: Arch. f. exper. Path. u. Pharm., 1902, xlviii, 331.

tion is slower in the first two hours; (5) when potassium nitrate or sodium chlorid is given with potassium iodid the excretion of iodine is distinctly greater. Broking¹³ found potassium iodid to be rapidly absorbed in the small intestine and the excretion in the urine to average 80 per cent. of that given. Excretion begins a few minutes after taking, and lasts in the urine sixty hours as a maximum. He found 75 per cent. excreted in the urine in the first twelve hours, and only 5 per cent. after that time, and found iodine in the feces only in traces. The relation between the excretion of chlorine and iodine, and particularly between chlorine and bromine has been studied by a number of observers. Sarvonat and Crenieu³⁴ have shown that animals on a chlorine free diet retain iodine in the tissues longer and in greater amounts than those receiving chlorides in the diet. The fate of the iodine which does not appear in the urine has not been entirely settled. Only small amounts appear in the feces, but iodine has been found in the perspiration, and in the hair, etc., and the thyroid may hold a considerable amount (*vide infra*). Boruttau¹⁹ found small amounts in the intestine, kidneys, heart and lungs four days after giving potassium iodid to a rabbit.

The iodized fats and fatty acids show the greatest difference from potassium iodid with regard to rapidity of excretion. After the administration of sajodin the iodine does not appear in the saliva and urine until after one to three hours, and eighty-four hours is required for excretion of iodine in the urine after a single dose, during which time 35 to 50 per cent. of iodine given appears in the urine (Broking¹³). From 7 to 10 per cent. appears in the feces unchanged. The highest point in the excretion is reached in the first twelve hours, but the amount excreted remains high during the first thirty-six hours, though in the case of potassium iodid it falls very low after twelve hours. Singer³⁵ found only 58.5 per cent. of iodine given as iodipin in the urine, and showed that the excretion was much slower than in the case of potassium iodid. Broking¹³ showed that the excretion of iodival began rapidly, reached its height within a few hours, and continued about sixty hours after a single dose, resulting in the excretion of about 80 per cent. of the iodine given. He showed that the rate of excretion was somewhat more uniform than with potassium iodid, especially when the drug was given in successive doses. He found 2 per cent. remaining in the feces. Loeb and van der Velden¹⁷ showed that iodival is rapidly absorbed and appears in saliva and urine in twelve minutes, and that the rate of excretion is practically parallel with potassium iodid. Loeb and van der Velden also showed that with lipoiodin the excretion began in two to three hours, and continued seventy-two to 120 hours, and they found an average of 3 to 12 per cent. in the

34. Sarvonat and Crenieu: *Compt. rend. Soc. de biol.*, 1911, lxx, 268.

35. Singer: *Ztschr. f. klin. Med.*, 1904, lii, 521.

feces under normal conditions. They also found some of the iodine present in the blood in ether-soluble form, and concluded that the ester or the free fatty acid was absorbed with iodine combined. Abderhalden and Hirsch³⁶ found that the ethyl esters of iodized fatty acids, such as lipiodine, were slowly absorbed. Loeb and van der Velden concluded that when lipiodine was given the iodine was slowly and evenly split off, giving a comparatively even iodine effect.

The iodized proteins, being of a more or less unstable character, are generally absorbed and excreted more rapidly than the iodized fatty acids, and the rate of excretion is more nearly like that of potassium iodide. Broking¹³ found iodoglucine to be excreted in a similar manner to iodine, and found 3 to 4 per cent. in the feces. I have found iodine in the urine within fifteen minutes after the administration of iodalbumin, which would be expected from its content of free iodine. The work of Taege, showing the relationship between the stability of the iodized proteins, has already been quoted (*vide supra*).

Metzger²⁶ studied the excretion of iodocitin (iodized lecithin) and found the highest point in excretion within the first twelve hours, a considerable amount being excreted in organic form.

The relation between iodine and chlorine excretion has been shown by Herzfeld and Heimann²⁷ to be the same in the case of iodostarin as when the iodides are given.

The influence of pathological conditions on the absorption and excretion of certain compounds has been studied by Loeb and van der Velden,¹⁷ who showed that in patients with diarrhea, 50 per cent. of iodine given as lipiodine may appear in the feces. Van der Velden³⁸ found that the excretion of iodine in the urine may be markedly changed from normal under certain pathological conditions. He found that there was a slowed excretion of potassium iodide, but a quickened excretion of iodine, and concluded that there may be a more rapid and intensive splitting of the iodine from the organic complex in the one case. The lessened excretion of iodine in nephritis has also been shown in the case of iodine by Norsa and Arcadi.³⁹

III.—DISTRIBUTION IN THE BODY

The factors concerned in the entrance of the various iodine compounds into the cell are still unsettled. O. Loeb⁴⁰ gave potassium iodide to rabbits, and found the largest amounts of iodine in the blood, kidneys and lymph-nodes (exclusive of thyroid). He found the brain, spinal cord, fatty tissues and bone always iodine-free. When he gave iodine, iodaniline and

36. Abderhalden and Hirsch: *Ztschr. f. physiol. Chem.*, 1911, lxxv, 38.

37. Herzfeld and Heiman: *Med. Klin.*, 1911, vii, 1858.

38. Van der Velden: *Therap. Monatsh.*, 1910, xxiv, 632.

39. Norsa and Arcadi: *Zentralbl. f. Biochem.*, x, 619.

40. Loeb, O.: *Arch. f. exper. Path.*, 1907, lvi, 310.

iodoform he found iodine in the brain and in fatty tissues, and he ascribed their entrance into these tissues to their lipoid solubility. Boruttau¹⁹ was unable to confirm his results with regard to potassium iodide, as he found iodine in the brain after giving potassium iodide. Boruttau found, four days after giving iodized proteins, that the largest amounts of iodine were in the brain. He concludes that the "Neurotropie" and "Lipotropie" of Loeb are relatively unimportant, except for iodized fats subcutaneously injected.

In this connection it is important to know in what form the iodine is present in the tissues. Lesser⁴¹ gave a rabbit 10 c.c. of 25 per cent. iodipin within twenty-four days, separated the fats from the tissues by ether extraction and obtained the following results:

Organ	Weight	— Mg. per Gram of Organ —	
		Total Iodine	I as Iodized Fat
Lung	26.4	0.55	0.255
Liver	68.0	0.45	0.1
Kidneys	18.2	0.2	0.009
Mesenterial fat	4.0	0.045
Blood	100 c.c.	0.15	trace

He concluded that on giving iodized fat a large amount of iodine was split off, and only a part circulated in the blood as fat or fatty acid, while a part is taken up by the tissues in the form of the fat or fatty acid.

To determine with what constituents of the cell the iodine is mainly identified after entrance into the tissues, I have analyzed certain tissues for the distribution of iodine in the cell, after giving iodized fatty acids, iodized proteins and potassium iodide. The liver was chosen for this work, as it is of convenient size (in rabbits) for extraction, and because it contains a considerable amount of lipoid substance, and also because it takes up a considerable amount of iodine. The separation of the cell constituents was made by the method described by W. Koch.⁴² The rabbits were given the iodine compound hypodermically or by stomach tube, and were later killed by bleeding from the neck, and the tissues collected and estimations of the total iodine in the principal organs made. The liver was cut up in small pieces and put in enough absolute alcohol to make 85 per cent. alcohol, with the water in the tissue, and allowed to stand for one to two weeks, after heating up to 70 C. for about an hour. It was then subjected to a continuous hot alcohol extraction in the extraction apparatus described by Koch, for four hours, followed by an ether extraction of one hour. The dried residue was then finely powdered, soaked up with water, made up again with absolute alcohol to 85 per cent. alcohol and allowed to stand a few hours, after which it was again extracted with hot alcohol for about twelve hours. The residue was then dried in

41. Lesser: *Arch. f. Dermatol. Syph.*, 1903, lxiv, No. 1.

42. Koch, W.: *Jour. of Am. Chem. Soc.*, 1909, xxxi, 1330.

an oven to constant weight. The alcohol extract was evaporated to near dryness, dried for two to three days in a vacuum desiccator and emulsified in water. After complete emulsification the lipoids were precipitated according to the method of Koch,⁴² by hydrochloric acid and chloroform. Estimations were made of the amount of iodine in the three fractions separated in this way ((1) protein residue, (2) lipoids—alcohol soluble, water insoluble, (3) water soluble, alcohol soluble). All iodine determinations were made by a slight modification of the method described by Hunter.⁴³ This method has given very uniform results in our hands.

The protocols of typical experiments will serve to illustrate the results.

Experiment V.—Potassium Iodid—Rabbit, weight 1,600 gm.

July 22, 3 p. m., 0.8 gm. KI in water by stomach tube.

July 23, 9 a. m., 0.5 gm. KI in water by stomach tube.

July 23, 10:30 a. m., killed by bleeding from neck.

Analysis of Tissues

Organ	Weight, Fresh, gm.	Mg. I per Gram Fresh Tissue
Kidneys	10.1	0.344
Blood	47.1	0.292
Heart	4.15	0.122
Liver	65.95	
Protein residue	0.000	
Lipoid (alc. sol., water insol.)	0.032 (32.0%)	
Alcohol soluble, water sol.	0.067 (67.0%)	
Total		0.099
Brain	8.95	0.007

Experiment VI.—Iodalbumin—Rabbit; weight 1,600 gm.

July 25, 3:00 p. m., 2 gm. iodalbumin in NaHCO₃ sol. by stomach tube.

July 26, 11:45 a. m., 2 gm. iodalbumin in NaHCO₃ sol. by stomach tube.

July 26, 2:00 p. m., killed by bleeding from neck.

Analysis of Tissues

Organ	Weight, Fresh, gm.	Mg. I per Gram Fresh Tissue
Kidneys	9.7	0.21
Blood	63.7	0.209
Heart	4.0	0.116
Liver	70.45	
Protein residue	0.000	
Lipoid (alc. sol., water insol.)	0.014 (24.5%)	
Alcohol sol., water sol.	0.043 (75.4%)	
Total		0.057
Brain	8.25	0.008

Experiment II.—Sajodin—Rabbit; weight 1,790 gm.

June 24, 0.3 gm. sajodin in olive oil subcutaneously.

June 25, 0.3 gm. sajodin in olive oil subcutaneously.

June 26, 9:30 a. m., 0.5 gm. sajodin in olive oil subcutaneously.

June 26, 1:30 p. m., killed by bleeding from neck.

43. Hunter: Jour. Biol. Chem., 1910, vii, 321.

Analysis of Tissues

Organ	Weight, Fresh, gm.	Mg. I per Gram Fresh Tissue
Heart	4.6	0.0276
Kidneys	10.82	0.0257
Lungs	9.12	0.0185
Liver	54.9	
Protein residue	0.0000	
Lipoid (alc. sol., water insol.)	0.0106 (62.7%)	
Alcohol sol., water sol.	0.0063 (37.3%)	
Total		0.0169
Blood	74.7	0.0151
Spinal cord	2.7	0.0078
Brain	7.85	0.0053

Experiment IV.—Sajodin—Rabbit; weight 1,400 gm.

July 17, 2:10 p. m., 2 gm. sajodin in olive oil by stomach tube.

July 18, 9:30 a. m., 2 gm. sajodin in olive oil by stomach tube.

July 18, 1:30 p. m., killed by bleeding from neck.

Analysis of Tissues

Organ	Weight, Fresh, gm.	Mg. I per Gram Fresh Tissue
Heart	3.2	0.178
Liver	49.5	
Protein residue	0.010 (6.4%)	
Lipoid (alc. sol., water insol.)	0.082 (52.9%)	
Alcohol sol., water sol.	0.063 (40.6%)	
Total		0.155
Blood	26.5	0.125
Kidneys	8.3	0.102
Brain	6.05	0.026

The results of these experiments would tend to show the following:

1. There are no essential differences in the distribution of iodid after giving potassium iodid and iodalbin, either in the distribution between the different organs, or in the distribution in the various constituents of the cell.

2. Sajodin produces a relatively higher percentage of iodine in the lipid fraction, indicating that the lipoids of the cell take up iodized fats from the blood. (More data are required on this point.)

3. The relative amount of iodine in the nervous tissues after sajodin is much greater than after potassium iodid or iodalbin — though small amounts of iodine have been found in all cases. The liver also stands relatively higher in iodine content after sajodin.

IV.—PHYSIOLOGICAL ACTION

The question of the physiological action of the organic iodine preparations is even more complex than that of the inorganic iodids, about which we know relatively little. In the case of potassium iodid, we have to consider the action of the salt itself, its *ions* after dissociation, and the free iodine which may be liberated in the body. In the case of an iodized

fat or protein we must consider the action of the molecule as a whole, its organic splitting products, the action of the iodine after liberation from the molecule and recombination in organic or inorganic form in the body. The last-named action would probably be identical with the action of iodine given in inorganic form. O. Loeb⁴⁴ divides the consideration of iodine action into three groups: (1) salt action, (2) effects on physiologic activity of thyroid and (3) changes produced in pathologic conditions. He assumes that iodism is due to the flooding of the organism with iodine *ions* by rapid absorption of potassium iodide, and advocates the use of iodized fats (lipiodine) since the iodine is gradually split off and "flooding" is avoided.

Erlenmeyer and Stein⁴⁵ conclude that all iodine action is *ion* action; that organic iodine compounds act only as iodine is split off in the body, and that such substances as iodipin and sajodin, by their smaller iodine content, are weak substitutes for potassium iodide. They regard iodism as an undesirable side action of *ion* action. Winternitz,⁴⁶ however, maintains that it has not been shown that the action of all iodine preparations is due entirely to *ion* action, or that iodipin and sajodin must be changed into potassium iodide to act, and he claims that iodism is much less frequent with the iodized fats. His contention is undoubtedly true, in that we may have other actions from iodized fats than the iodine *ion* action; but we have no evidence that the action so produced is the action desired in the cases in which the drugs are recommended as substitutes for potassium iodide.

With regard to the question of iodism, v. Notthafft⁴⁷ concluded that the diminution in frequency of observation of iodism with the organic iodine preparations was always associated with other disadvantages, or that they had a feebleness of activity, and the substances either split off too little iodine, or split it off with greater difficulty.

The relation of iodine content to thyroid activity has been known since Baumann⁴⁸ published his observations on the iodine content of the gland. Up to the present time the nature of the iodine complex in the gland is not known. Hunt and Seidell⁴⁹ attempted to find thyrotropic iodine compounds, testing them physiologically by the aceto-nitrile test. The only iodine compound, except that obtained from thyroid, shown to have any specific "thyroid" action was that from "bladderwrack," and that was much weaker in proportion to its iodine content than the thyroid

44. Loeb, O.: *Deutsch. med. Wchnschr.*, 1911, xxxvii, 1006.

45. Erlenmeyer and Stein: *Therap. Monatsh.*, 1909, xxiii, 133.

46. Winternitz: *Therap. Monatsh.*, 1909, Part 8.

47. Von Notthafft: *Monatsh. f. prakt. Dermat.*, Oct. 15, 1910; abstr. in *Jour. Am. Med. Assn.*, lvi, 685.

48. Baumann: *Ztschr. f. physiol. Chem.*, 1895, xxi, 319.

49. Hunt and Seidell: *Jour. Pharm. and Exper. Therap.*, 1910, ii, 15.

substance itself. All other organic compounds studied were found to be relatively only about as active as potassium iodid, and they ascribe their action to their indirectly increasing the activity of the thyroid by increasing its iodine content. V. Fürth and Schwartz⁵⁰ tested the action of iodized egg albumin when administered intravenously and found an action similar to that of iodothyron, i. e., it produced a fall in blood-pressure both before and after sectioning the vagi. No other thyroid activity, however, has been shown for it.

The giving of iodine in combination with other substances may sometimes lead to toxic action due to the rest of the molecule. This has already been pointed out for iodoform and its substitutes. Other substances, however, intended for use for their iodine content have shown a toxicity far greater than that of potassium iodid. Eeckhout⁵¹ has shown iodoval to have a hypnotic action, similar to that of bromural. Loeb and van der Velden¹⁷ have shown that iodoval is fatal to rabbits in doses of 0.5 gram per kilo weight. It is obvious, therefore, that such toxic compounds could not be used where the action of large amounts of iodine was desired. Boulaire⁵² tested the comparative toxicity of various iodine compounds and found the iodized fats least toxic, both as to immediate and late effects, while he found iothion most toxic. (Iodoval was not tested.)

V.—CLINICAL REPORTS

As is to be expected, we have numerous reports of the use of various organic iodine preparations in practically every disease in which iodine or the iodids are recommended. Many writers have claimed that iodism is less frequent when an iodized fat, for example, is used in place of potassium iodid. We find, however, that in nearly every case these substances have been given in relatively small doses, and very few attempts have been made to increase the dose rapidly, as is often done with potassium iodid. One reason for this is undoubtedly the almost prohibitive cost of the organic preparations, when large amounts are desired.

Many observers have also shown that the stomach is less apt to be disturbed by the administration of organic compounds. This is to be expected when substances not acted on by the gastric contents are given, when the substances are not irritating themselves. In the case of commercial preparations containing free iodine we should not expect them to pass through the stomach without local effect.

Winternitz,¹⁶ O. Loeb⁴⁴ and Boruttau⁵³ agree that the organic iodine preparations are not to be regarded as substitutes for the alkalin iodids in every case, but that each class of compounds has its own special con-

50. Von. Fürth and Schwartz: *Pflüger's Arch.*, v, 125, p. 113.

51. Eeckhout: *Arch. f. exper. Path. u. Therap.*, 1907, lvii, 338.

52. Boulaire: *Compt. rend. Soc. de biol.*, 1906, lvi, 303.

53. Boruttau: *Deutsch. med. Wehnschr.*, 1911, No. 43, p. 1975.

siderations which should be taken into account in the use of any of them. Winternitz¹⁸ recommends the use of iodipin in such cases as bronchial asthma, arteriosclerosis (luetic endarteritis) and lead-poisoning, on account of its slow splitting and prolonged excretion, and states that its use in special cases is well founded. The same considerations also apply to the other members of the iodized fat and fatty acid group, according to their relative rates of absorption, and excretion. We have less physiological grounds, however, for the giving of iodized proteins.

VI.—CONCLUSIONS

From the evidence presented above as to chemical nature, absorption and excretion, distribution, physiologic action and clinical results, we may draw the following conclusions with regard to the therapeutic uses of the organic iodin compounds:

1. Up to the present it has not been shown that the organic iodin preparations, with the exception of preparations of thyroid, have any specific action in pathologic conditions, except the action of iodin after separation from the molecule.

2. The iodized proteins seem to be of advantage for therapeutic use only in so far as they avoid gastric irritation. The more stable compounds are apparently not entirely split in the body and are therefore not well utilized, while the less stable compounds have no advantages over the alkaline iodids, either as to local effects, or as to rapidity of absorption and excretion.

3. The iodized fats and fatty acids appear to have some advantage when the continuous action of small amounts of iodin is desired. They are more slowly and evenly split, and the amount of available iodin in the blood does not vary from time to time to the extent that it does when the alkaline iodids are administered. The use of the iodized fats in such conditions as arteriosclerosis, bronchial asthma, lead-poisoning, etc., probably has some rational basis, therefore, on physiologic grounds. These substances are also as a rule non-irritant to the stomach.

4. The difference in frequency of iodism is probably due to the difference in the amount of available iodin present in the body at any one time. When large amounts of iodin are desired, as in cerebrospinal syphilis, avoiding the danger of iodism would be at the sacrifice of therapeutic efficiency.

5. The use of organic iodid preparations with toxic side actions, due to the molecule or its splitting products, should of course be discouraged. The products of iodin with the higher fats and fatty acids are generally free from toxic actions.