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[Reprinted from THE MEDICAL NEWS, June 29, 1895.]

THE PHYSIOLOGIC AND THERAPEUTIC ACTION OF IRON, WITH A DISCUSSION OF ITS NEWER PHARMACEUTIC COMPOUNDS.[1]

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A KNOWLEDGE of the physiologic compounds of iron and of the food-stuffs is necessary to any clear conception of the therapeutic use of iron. Bunge some ten years ago (*Zeitschrift für Physiol. Chemie*, 1885) found an iron-holding organic compound in the egg-yolk, in milk, etc., which was very stable. At the body-temperature it yielded only after a couple of hours the iron-reaction to ammonium sulphid. This compound he named hematogen, from the belief that it is the antecedent of hemoglobin. Zelewski (*Zeitschrift für Physiol. Chemie*, 1887) obtained from the liver a similarly stable iron-holding compound which he named "hepatin." This contained less iron than hematogen—the former 0.011 per cent.. while the latter held 0.29 per cent.

Bunge, in the paper describing his observations, advanced a novel theory of the beneficial action of iron in anemia. Recognizing at once that as the animal economy received in the food stable organic iron-compounds there existed no call in the animal organism for synthetic processes. His investigations tended to disprove that iron was of any further use than as a pro-

[1] The address in therapeutics at the Ontario Medical Association, held June 5 and 6, 1895.

tective agent to hematogen by uniting with reagents like H_2S that would attack the iron in the latter, and thus permit it to escape.

Further studies soon showed that hematogen belongs to the nuclein class of proteids. Macallum ("On the Demonstration of the Presence of Iron in Chromatin by Microchemical Methods," *Proceedings of the Royal Society*, vols. l and lvii; "Studies on the Blood of Amphibia," *Transactions of Canadian Institute*, vol. xi; and "On the Absorption of Iron in the Animal Body," *Journal of Physiology*, vol. xvi, Nos. 3 and 4, 1894) by the use of microchemic technique showed that iron is a constant constituent of the chromatin (nuclein of chemists) of all vegetable and animal cells.

The statement that hemoglobin arises from a breaking down of the chromatin of the nucleus of the hematoblasts is supported by a mass of weighty evidence. Researches at the present time go to show that nuclein forms an endless series of compounds with albumin, and that it itself is as varied as the organ or tissue from which it is obtained. The amount of iron seems to vary with the nuclein, and it is possible that it is absent in some, as claimed by Halliburton (Croonian Lectures, 1893).

There is no evidence that the animal body can elaborate nucleins; these are always the finished product of plant-life. It must be clearly understood that the chemic composition of these nucleins as found by different investigators differs so much that some chemists are inclined to deny a chemic individuality to the substance, and that the isolated substances do not represent the living chromatin any more than does serum-albumin represent living protoplasm. Physiologic and pathologic research shows that free hemoglobin and its disintegration-products are undoubtedly never elaborated into nuclein or chromatin again, and hemoglobin free in the blood or administered as food cannot be of further use as an "oxygen-carrier." The most careful researches on

hemoglobin indicate that it is invariably destroyed by the liver, and its iron separated as a free inorganic compound. By the administration of large doses of inorganic iron-compounds the liver, the intestinal mucosa, and even the renal parenchyma are found to be loaded with inorganic iron. In the case of some animals, if the dose is large enough, a fatal result takes place by coma, suggesting that free iron is the causation possibly of the coma often seen terminating pernicious anemia. By the use of large doses of hemoglobin a condition of the liver, the intestinal mucosa, and the kidneys can be induced similar to that which follows large doses of inorganic iron—even the iron-coma.

Iron is undoubtedly absorbed, and its good results when administered hypodermically and by the rectum, as well as the beneficial effects following the use of iron sulphid, give a complete answer to Bunge's contention that the therapeutic action of iron is purely that of a protector to nuclein.

Conceding as we must that iron-salts, and even organic compounds other than chromatin, are not elaborated into "oxygen-carriers," some tonic, stimulative, alterative, or protective action must be ascribed to this drug. Does it increase absorption and assimilation of chromatin or stimulate the conversion of the chromatin of the hematoblasts into hemoglobin, or both? We would be in a position to answer could we offer a clear explanation of the action of arsenic as a blood-former—no doubt the two drugs bear a strong analogy in their therapeutic action. The unpleasant gastro-intestinal effects from the use of iron, not infrequently noticed in clinical work, probably arise from hepatic disturbance set up by the free iron in the liver-parenchyma. The combination of minute doses of mercury with the iron appears to make the latter tolerated, although when taken alone it is very offensive.

The broad indications for the use of iron may be not

only those of primary and secondary anemia, but conditions of asthenia following or accompanying such diseases as pneumonia, septic infection, erysipelas, diphtheria, etc. It is not intended, however, to point out here the special diseases in which iron is indicated. Proceeding at once to the promised criticism of the newer pharmaceutic preparations, our attention can profitably be confined to the following principal ones: "Albuminate of iron," "peptonate of iron," "hemoglobin" (including hemoferrum), "ferratin," and "bone-marrow."

Iron albuminate is an artificial preparation of iron in weak chemic union with albumin. "Ammoniacal solutions of artificial albuminate of iron change their color almost instantly on the addition of sulphid of ammonium" (Bunge, *Physiological Chemistry*, translated by Wooldridge, p. 102). Iron albuminate cannot be converted into nuclein any more than iron oxid, and therefore can have no more therapeutic value than the latter. Inasmuch as nuclein cannot be converted into an ordinary peptone by any amount of digestion, "peptonate of iron" possesses no more value than "albuminate of iron," and, what is worse, the drug usually sold under this name appears to be nothing more than iron citrate dissolved in a peptonic mixture. The addition of ammonium sulphid to the "peptonate of iron" will instantly throw out the iron as an inky precipitate.

Hemoglobin is found in the market as "dried ox-blood," "hemoferrum," etc. The entire weight of evidence goes to show that this compound after absorption is doomed to destruction by the liver, its iron being separated out as an inorganic compound ultimately. Except in the way of furnishing an increase of the pigments of the organism (viz., bile, urine, etc.), the therapeutic action of hemoglobin is similar to that of any iron-salt.

Ferratin was made originally from pigs' livers.[1] This

[1] Finely minced pigs' livers are treated with water, and the mass raised gradually to the boiling-point, and kept at that tem-

is not a nuclein-compound. The ferratin in our market is made from the union of albumin and iron in an alkaline solution.[1] The claim put forth that this latter drug is almost identical with Bunge's hemoglobin is, to say the least, most extraordinary. Ferratin contains 7 per cent. of iron and no phosphorus; in hematogen the iron amounts to 0.29 per cent. and phosphorus is present. An ammoniacal solution of ferratin changes color instantly on addition of ammonium sulphid, indicating that it is a simple albuminate of iron (Bunge, *Physiological Chemistry*, translated by Wooldridge, p. 102). The addition of ammonium sulphid to the dry powder gives the iron-reaction also instantly. The fact that a compound containing 7 per cent. of iron is a very improbable antecedent of hemoglobin, which contains less than 0.5 per cent., would suggest itself at once. It has already been pointed out that hemoglobin has a

perature for a few minutes. The filtered fluid when cool gives on the addition of acetic acid a flocculent precipitate which quickly settles and can be easily washed on the filter. It contains on the average 6 per cent. of iron. This is the original ferratin. F. Vay: "Ueber den Ferratin und Essingchal dies Leber," Zeitschr. für Physiol. Chemie, vol. xx, p. 377.

[1] One mixes 100 grams of albumin in 2000 c.cm. of cold water, with a solution of 25 grams of ferric tartrate in 250 c.cm., and neutralizes with soda—viz., 38 grams of caustic soda diluted to 10 per cent. The brownish-yellow fluid is warmed for from two to four hours at 90° C., when it becomes clear. It is allowed to cool, and then it is acidified with tartaric acid and rendered alkaline with ammonia. After twenty-four hours' treating at 90° C. it is cooled and the ferratin precipitated with tartaric acid. The precipitate is washed on the filter and dried between paper.

In order to purify it, it is again dissolved in 1400 parts of water with 20 parts of ammonia (25 per cent. solution) and 20 parts of 10 per cent. solution of ammonium tartrate. It is then warmed for twenty-fours at 90° C. and then the ferratin precipitated, washed, and dried as before. From De Filippi, "Experimental Untersuchungen über das Ferratin von Marferi, Schmiedeberg," Ziegler's Beiträge zur Pathologischen Anatomie, vol. xvi, p. 462.

definite antecedent, a nuclein-compound containing a certain amount of iron. Much of the nuclein of the animal body is in union with albumin in the compounds known as nucleo-albumins. The amount of iron in these varies with the organ or tissue from which they are obtained.

Until the peculiar nuclein that acts as the antecedent to hemoglobin can clearly be determined it is useless to administer any nuclein simply because it is a nuclein, and it is more rational to depend upon "bone-marrow." The nucleins of bone-marrow may in all probability be the pharmaceutic preparation of the future. By extracting the fat and by digestion of the albuminous elements, the bone-marrow nucleins could be obtained almost pure. Prepared in this way their administration in a concentrated form would be possible, and a disappearance of the weak and offensive-looking preparations now in the market would soon occur.

In this connection I may mention that Gourlay (*Journal of Physiology*, vol. xvi, p. 23) has concluded that the active physiologic remedy in the thyroids is a nucleo-albumin.

It is very possible that the nuclein alone of the colloid substances will yet prove itself the active ingredient in the thyroid preparations.