phenomena we have presented. The activator either converts an inactive pro-hormone in the hypophysis to an active form or else is able actually to convert the growth hormone into the gonad-stimulating one. It is attractive to strike an analogy here with the conditions found in the interaction of certain ferments and their co-ferments, for example the interaction of trypsinogen and enterokinase to produce tryptase, or again the cooperative action of the lactic-acid-forming enzyme with its co-ferment.

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Ionic Migration of Bismuth in Different Bismuth Products Under Different Conditions.

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Cerebral and spinal fluid penetration has not been established with certainty for all products of bismuth, and the efficacy of bismuth in cerebrospinal syphilis has been asserted and denied. It is conceivable that the variations here might be related to the amphoteric character of the metal which would vary with the product used. That is, penetration and activity might be favored by anionic bismuth, in accordance with the well-known composition of cerebrospinal fluid in which anions exist in relatively higher concentration than cations, and with the well-known appearance of the anions bromide, iodide and salicylate in this fluid. Correlated with these phenomena are the demonstrated penetration of the anionic bismuth compounds, sodium bismuthate and sodium iodobismuthite, and the negative or undependable penetration of the cationic bismuth products, bismuth metal, bismuth salicylate and potassium bismuth tartrate, previously reported from this laboratory.[1] Since the ionic character of bismuth in iodobismuthite only had been established in our previous work, the other products having been accepted on theoretical grounds, it appeared desirable to establish experimentally the ionic character of bismuth in various products under different conditions. Some of these products are claimed to penetrate the brain, and have been accepted for *New and Non-official Remedies* since our original work.

[1] Hanzlik, Mehrtens, Gurchot and Johnson, *J. Am. Med. Assn.*, 1931, in press; Gurchot, PROC. SOC. EXP. BIOL. AND MED., 1930, **27**, 509.

Six different products of bismuth were tried, in aqueous solution (really after hydrolysis of some products), in special media such as 25% sucrose (bismuth sodium tartrate), 6% dextrose (bismuth metal) and ethylene glycol and alcohol (sodium iodobismuthite) and in dialyzed and natural horse serum. The bismuth-mixture was introduced into a convenient glass U-tube of 10 cc. capacity up to the level of the stop-cocks, one in each arm. Both cathode and anode chambers were filled with a non-conducting fluid, *i. e.,* distilled water, one of the special media mentioned above, or serum. Platinum electrodes and a current of 110 volts were used, but only from 10 to 45 millivolts passed through the bismuth-mixtures. Generally the current was passed through for 5 hours, but occasionally 3 hours and 26 hours. Incubations at 37.5°C. for 24 hours were made with the highly insoluble bismuth metal, bismuth salicylate and bismuthate in serum, in addition to the use of fresh serum-mixtures of these products. Saturated solution of hydrogen sulphide in water was added to each chamber and the presence of bismuth recognized by a black precipitate; in the case of iodobismuthite also by the presence of the colored ion which was photographed in color. At least 3 experiments were made with each product and condition; the results agreed invariably. The following tabulation gives a summary of the results obtained and a correlation with cerebral penetration as demonstrated by us or as claimed by others.

It is seen that the ionic character of the bismuth varied with the compound and with the conditions, thus indicating the complex behavior of bismuth. In bismuth metal, bismuth was found to be electropositive, as might be expected, and this was not changed in standing and incubated serum. Bismuth salicylate yielded a small amount of electropositive bismuth in incubated serum only, but the white aggregates moved to the cathode in both water and serum. These products are poorly absorbed and did not demonstrably, or at least dependably, penetrate the brain. In sodium bismuthate, the bismuth is obviously electronegative, but the product is so insoluble that, even after incubation in serum, bismuth ions were not demonstrated although yellowish aggregates moved to the anode (electronegative); bismuth was demonstrated in rabbit brains.[1] In sodium iodobismuthite, the bismuth was electronegative and combined with iodine, since the complex colored ion migrated without decomposition, in both aqueous media and serum: this bismuth has been demonstrated in animal brains and human cerebrospinal fluids[1] and its absorption is good. Bismuth sodium tartrate gave interesting results, since it yielded either electronegative or electropositive

TABLE I.
Electrical charges carried by bismuth in different bismuth products and cerebral penetration.*

Product	In Aqueous Medium	In Serum	Cerebral and Spinal Fluid Penetration
Bismuth metal (Bi)	+ = dextrosesol. + = water	none = fresh + = incubated + = stood 22 hr.	undependable or not demonstrable
Bismuth salicylate ($BiOC_7H_5O_3$)	None = water (+ = aggregates)	none = fresh + = incubated (+ = aggregates)	undependable or not demonstrable
Sodium bismuthate ($NaBiO_3$)	None = water (— = aggregates)	none = fresh none = incub. (— = aggregates)	demonstrated
Sodium iodobismuthite (Na_2BiI_5)	— = water — = ethylene glycol	—	"
Sodium bismuth tartrate ($Na(BiO)_4Tart$)†	+ = sucrose sol. + & — = water	—	claimed
Sodium bismuth thioglycollate ($Bi(SCH_2CO_2Na)_3$)‡	— = water	—	"

* The plus sign (+) means electropositive (cation), and the negative sign (—), electronegative (anion).
† Product marketed by Searle and Co., Chicago.
‡ Product marketed by Parke, Davis and Co., as Thiobismol.

bismuth, or both. In 25% sucrose solution, containing a trace of NaOH, the product gave electropositive bismuth only, but after hydrolysis of this solution by direct treatment with water, there were electronegative bismuth and electropositive bismuth, in 1 experiment the ratio being about 1:4, respectively. In serum, the bismuth sodium tartrate gave electronegative bismuth only; this product was found to penetrate the brain of animals, but not cerebrospinal fluid in man; absorption was good. However, the literature on the tartrates of bismuth is contradictory. The bismuth of bismuth sodium citrate ($Na(BiO_2)Ci$), which is chemically analogous to bismuth sodium tartrate, is claimed to be anionic[2] and cationic.[3] Both claims may be correct, for this compound may contain either electropositive or electronegative bismuth, or both, according to the treatment it may be given. Sodium bismuth thioglycollate, in both water and serum, yielded electronegative bismuth only, the quantity being comparatively small; this bismuth is claimed to penetrate the brain.[4] It is possible that, in serum, some of the

[2] Oettingen, Ishikawa and Sollmann, *J. Am. Pharm. Assn.*, 1928, **17**, 124.
[3] Morton, *Quar. J. Pharm. Pharmacol.*, 1930, **3**, 561.
[4] Gruhzit and Sultzaberger, *Am. J. Syphilis*, 1927, **11**, 103.

products formed bismuth complexes. Changes in chemical reaction might affect the results, but were not considered, the products being used as in therapeutics.

Conclusion. The amphoteric character of bismuth in 6 different products used in the treatment of syphilis, and variations in the behavior of the metal under different conditions, were demonstrated. These properties are believed to be of significance for the pharmacological and clinical actions of bismuth, such as absorption, toxicity, cerebral penetration, activity in cerebrospinal syphilis, etc. Correlation appears to exist between cerebral and spinal fluid penetration, and the electronegative (anionic) character of bismuth, which is consistent with the comparatively greater penetration of other anions than cations.

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Streptococcus Leucocidin and the Resistance of Clasmatocytes.

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Although long known (Ruediger[1]), the leucocyte destroying properties of virulent hemolytic streptococci have never been as fully investigated as they deserve. We agree with McLeod[2] that leucocidin formation is perhaps the most important factor in the virulence of this micro-organism. We have recently undertaken a more complete analysis of leucocidin which we believe is the first since that of Channon and McLeod.[3] The only other study that is at all complete is that of Nakayama.[4]

The presence of leucocidin in a broth culture of streptococcus is evidenced by the demonstrable disintegration of leucocytes that are exposed to it, or better, by interference with the oxygen absorption of these cells when living as contrasted by its absence when they are dead. This change is delicately measured by the methylene blue bioscopic test of Neisser and Wechsberg.

The precise mode of action of leucocidin under conditions of in-

[1] Ruediger, *J. Am. Med. Assn.*, 1905, **44**, 198.

[2] McLeod, *J. Path. and Bact.*, 1914, **19**, 393.

[3] Channon and McLeod, *J. Path. and Bact.*, 1929, **32**, 283.

[4] Nakayama, *J. Inf. Dis.*, 1920, **27**, 270.