DISTRIBUTION OF MITOCHONDRIA IN THE FORAMINIFERAN, IRIDIA DIAPHANA

IT has been occasionally noted[1,2] that the mitochondria in a cell are arranged in greatest numbers at the locus of interchange of metabolites between the cell and its environment. A review of the morphology of glandular cells[3] reveals that mitochondria are most numerous in the basal regions of such cells and that it is in these regions that metabolites are absorbed. Doyle has carried this a step further to suggest that in *Amoeba* the mitochondria function as transportive elements within the cell.

The structure of *Iridia diaphana* is significant in this regard. The organism is abundant on *Posidonia* (turtle grass) at Dry Tortugas, Fla. It is an arenaceous form which is particularly adapted to cytological research because it frequently leaves its shell and crawls about naked.

The cytoplasm contains a large nucleus, numerous golden or reddish oil droplets 2 to 5 micra in diameter, many colorless carbohydrate spheres 3 to 6 micra in diameter, numerous minute calcium oxalate crystals not over ½ micra long, and ovoid mitochondria which average ¾ micra in length. The crystals and the mitochondria are the only structures which might be confused with each other because of their size and appearance. They are readily differentiated in the living condition by means of polarized light. The crystals are brilliantly optically active, whereas the mitochondria are not noticeably so.

In the central protoplasmic mass, from which myriads of anastomosing filamentous pseudopodia extend, there are many currents of streaming protoplasm constantly in action. These currents frequently lead to the bases of pseudopodia at which points only the mitochondria flow out into the hyaline cytoplasm. The mechanism whereby the constituents are segregated so that only the mitochondria leave the central mass when there are other equally small bodies present which never do is entirely unknown. The mitochondria, which are frequently larger in cross section than the cross section of the pseudopod, flow out into the pseudopodia and in so doing meet and pass other mitochondria which are returning to again mingle with the other cytoplasmic constituents of the central mass.

Whatever the rôle of the pseudopodia; whether elimination of waste products, absorption of food or as contractile elements; they are always liberally supplied with mitochondria, and mitochondria are the only formed bodies in them. Conversely, whatever the rôle of the mitochondria, their presence in the pseudopodia gives them ample opportunity for the interchange of substances with the surrounding medium.

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[1] Horning, *Austral. Jour. Exp. Biol. and Med.*, 2–5, 1925–28.

[2] Doyle, Dissertation, The Johns Hopkins University. In press.

[3] Bowen, *Quart. Rev. Biol.*, 4: 1929.

DIRECT ISOLATION OF PASTEURELLA-LIKE MICROORGANISMS FROM BRAINS OF HORSES SUFFERING FROM SO-CALLED CORNSTALK DISEASE

IN a recent note in SCIENCE[1] mention was made of the isolation of pasteurella-like microorganisms from the brains of seven horses that succumbed to so-called cornstalk disease in different counties in Illinois. These isolations were made following death of guinea pigs, pigeons and rabbits inoculated subcutaneously with horse brain tissue suspended in sterile physiological sodium chloride solution, as well as saline suspensions of mixed aerobic cultures from brains of naturally infected horses. For the reason that laboratory animals may harbor pasteurella and, following death from a variety of causes, yield positive cultures, the brains of horses dying from so-called cornstalk disease were cultured on different media to appraise the part laboratory animals might play in the positive pasteurella isolations following inoculation with horse brain tissue and mixed cultures from horse brain suspended in saline.

Each horse supplying brain tissue included in direct cultural studies, as in aforementioned studies, displayed a spontaneous encephalitic syndrome. The affected horses originated on different farms over a territory extending from north-central Illinois south more than 150 miles to the south-central district of the state, including Will, Iroquois, Champaign, Christian, De Witt, Douglas and Montgomery counties. The horse brains were delivered to the laboratory in from one to six hours following humane destruction or death from so-called cornstalk disease. Immediately on arrival the encephalon was removed from the cranium and the meninges dissected from the brains. Small pieces of the brain tissue were seeded in tubes of pork and beef meat mash broth. The inoculated tubes were allowed to incubate for three to six days at 37° C. Gentian violet agar plates were then streaked from the meat mash cultures with a platinum loop. Colonies resembling pasteurella developing along the line of inoculation were picked on 10 per cent. horse blood agar slants for identification.

From eight different horse brains pasteurella-like microorganisms were isolated by direct cultural methods. Similarly streaked cultures of the meat mash horse brain cultures on plain and blood agar plates were invariably overgrown with a variety of uniden-

[1] SCIENCE, 81: 2093, 153, February 8, 1935.

tified bacteria, including gram positive rods, *E. coli*, streptococci and diplococci, as well as actinomyces, aspergilli and other unidentified molds.

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ERGOTOCIN

IT has been found by the authors, working in conjunction with Drs. Davis, Adair and Rogers, of the Department of Obstetrics and Gynecology of the University of Chicago, that the alkaloids ergotoxine, ergotamine, sensibamine are uniformly ineffective when administered orally to human mothers in doses of 2 mg. Larger doses (2–4 mg) often induce unpleasant side reactions such as nausea, vomiting, increase in blood pressure, diarrhea, etc. However, even these large and dangerous doses do not induce contractions in the eighth-day postpartum uterus, in all mothers. While the number of cases studied by us is relatively small (15 cases) these large doses of the alkaloids were found effective only in about 30 per cent. of the cases.

We have found, however, that some fluid extracts of ergot, prepared in accordance with U. S. P. method, were effective in doses corresponding to 3–4 gm of ergot. The activity of these extracts could of course not be due to the known alkaloids (the amounts of these alkaloids as assayed by us were too small to account for the activity), and we undertook the problem of the isolation of the principle responsible for the efficacy of oral ergot dosage. While preparations containing from 60 to 80 per cent. of this principle were obtained by us over a year and one half ago, the isolation of the pure crystalline substance was made only on December 12, 1934. We have called this principle ergotocin. In human mothers this substance is uniformly effective when administered orally in doses of 0.3 mg and intravenously in doses as low as 0.1 mg. The yield of 0.3 mg of ergotocin is roughly equal to from 3 to 4 gms of crude defatted ergot. This principle thus accounts for the activity of the fluid extracts.

Ergotocin has now been used on over 150 patients and no unpleasant symptoms have been observed with it. It controls uterine hemorrhage instantly. Intravenously the effect is noticed within 15 seconds after administration. In the first stages the action of ergotocin resembles that of pituitary extracts, except that its effect lasts for 3 or 4 hours, in marked contrast to the transient effect usually obtained with pituitary extract. In its low toxicity, small dosage, prompt action in uterine hemorrhage, prolonged effect on the uterine muscles, ergotocin is unique among oxytocic principles.

Ergotocin salts, as well as the free base, are white, well-defined crystalline substances. The base melts with decomposition at 155°. The picrate, which is red, melts at from 195 to 197°, with decomposition. The free base is somewhat soluble in water, and the salts are readily soluble. One may obtain even a 10 per cent. aqueous solution of some salts of ergotocin, a unique property among the alkaloids isolated from ergot. Ergotocin differs from the known ergot alkaloids (ergotoxine, ergotamine, sensibamine) in that it is not precipitated by Meyers's reagent in dilutions greater than 1 part in 7,500, while the other alkaloids are precipitated in dilutions of 1: 200,000, to 1: 2,000,000. The optical rotation of the salts of ergotocin so far investigated is positive. The chemistry of ergotocin as well as some of the attempts to synthesize it will be reported as soon as the work now under way is complete.

We believe that with the isolation of this principle ergot therapy can now be put on a rational basis. If one bears in mind that many ergots do not contain this principle (and yet are acceptable on the basis of the U. S. P. assays), the cause of the difference of opinion among obstetricians regarding the value of ergot in obstetrics becomes evident.

The authors wish to take this opportunity to thank most sincerely the Research Corporation, Inc., for a grant which made this work possible and the Eli Lilly Company for generously aiding us in this investigation.

Needless to say, without the cooperation and constant guidance of Drs. Davis, Adair and Rogers, on the clinical and pharmacological evaluation of this principle, this work would not have been brought to a successful conclusion.

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