Bei den xenoplastischen Experimenten früherer Autoren (HOLTFRETER, ROTMAN, WAGNER[1]) waren chimärische Haftfäden entstanden, in denen das axiale Mesenchym gemischten Charakter hatte, die epidermale Wand aber rein Triton war. Die hier vorliegenden Chimären gehen in der Mischung weiter, indem auch die Epidermis chimärisch aufgebaut ist.

Es ist eine allgemeine Erfahrung, daß *induzierende* Faktoren nicht artgebunden sind, sondern sich bei größeren systematischen Gruppen vertreten können. Weniger klar aber ist bis jetzt, in welchem Grade auch die *reagierenden* Gewebe allgemeine vertretbare morphogenetische Fähigkeiten besitzen (vgl. BALTZER[2]). Die vorliegenden Versuche wurden unternommen (und werden fortgesetzt), um Material zu dieser Frage beizubringen. Dabei soll hier gerade die Entwicklung eines Organes analysiert werden, dessen Homologie in den beiden Ordnungen bestritten ist, das in den beiden reinen Arten zwar ähnliche Funktion hat, aber verschieden gebaut ist und eine verschiedene Entwicklung durchläuft[3].

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Zoologisches Institut der Universität Bern, den 2. Januar 1951.

Summary

Chimeric adhesive organs produced by xenoplastic ectodermal transplantations between *Bombinator* and *Triton* germs are described. The adhesive organs are very different in the two amphibian groups. The projecting rod-shaped balancer of the *Triton* larva is formed by two epidermal layers and an axial mesodermal core (mesectoderm), while the flat adhesive sucker of the young *Bombinator* tadpole consists mainly of one epidermal layer of secretion cells. Probably the two organs are either non-homologous, or the homology is partial only. Nevertheless, in the chimeras young balancers are formed, the epidermal layers and the mesectoderm of which are provided in part by *Triton* and in part by *Bombinator*.

[1] G. WAGNER, Rev. suisse Zool. *56* (1949); dort genauere Literatur.

[2] F. BALTZER, Rev. Suisse Zool. *57* (1950).

[3] Die Arbeit wurde mit Hilfe der Dr.-JOACHIM-DE-GIACOMI-Stiftung der Schweizerischen Naturforschenden Gesellschaft ausgeführt.

Antagonism between Streptomycin and Para-Aminosalicylic Acid

Para-aminosalicylic acid (PAS) has attracted much attention as an antitubercular agent, effective by itself and even more so when administered with streptomycin. The rapidity with which Mycobacteria develop resistance to streptomycin is well known; they may also become resistant to PAS[1]. However, concomitant exposure to both drugs prevents development of resistance to either one[2].

Although Mycobacteria appear to be especially sensitive to PAS, *Escherichia coli* may be used conveniently as a test organism to study the interaction between PAS and streptomycin *in vitro*[3].

The present report emphasizes the importance of relative concentrations of PAS and streptomycin in determining the response of streptomycin-sensitive organisms to mixtures of the two drugs and the antagonism between PAS and streptomycin acting together on a streptomycin-resistant strain derived from an originally sensitive culture.

[1] G. IVÁNOVICS, Exper. *6*, 108 (1950).

[2] A. DELAUDE, Paris Médical *40*, 458 (1950).

[3] K. J. DIVATIA, J. DUFRENOY, and R. PRATT, J. Amer. Pharm. Assoc., Sci. Ed. *39*, 170 (1950).

Experimental

From a strain of *E. coli* initially sensitive to streptomycin (growth prohibited by 7 μg/ml), we secured, by repeated sub-culturing in increasing streptomycin concentrations, a strain which, if given sufficient time, grew in broth containing 300,000 μg of streptomycin per ml. This strain was not streptomycin-dependent, since it grew well in broth lacking streptomycin.

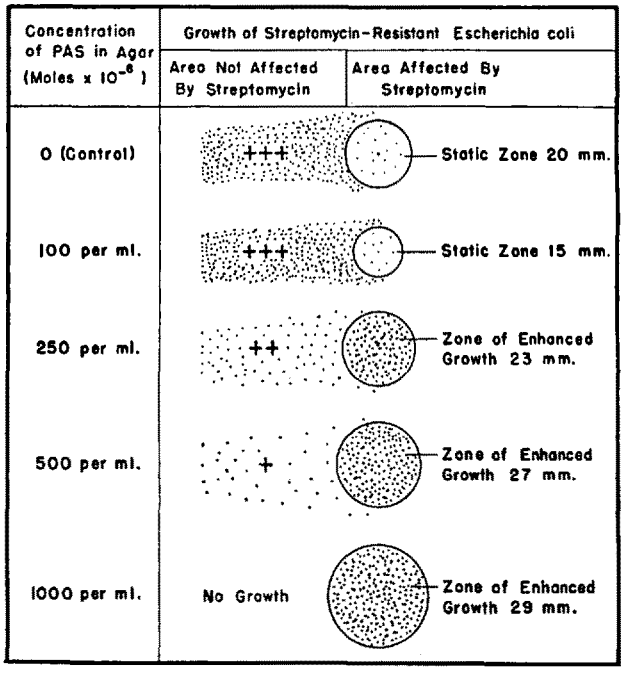


Fig. 1. – Diagrammatic representation of growth response of a streptomycin-resistant strain of *Escherichia coli* in cylinder plate tests when different amounts of PAS were incorporated in the agar. Cylinders (not shown) contained solutions of streptomycin (50,000 μg/ml) in buffer. Only a small segment of the agar surface, including the area in which growth was affected by streptomycin and part of the adjacent unaffected area, is diagrammed. Heavy, medium, and light growth in the background areas are represented by +++, ++, and +, respectively. See text for further explanation.

Using a modified cylinder-plate technique[1], we seeded nutrient agar plates containing different concentrations of PAS with 1 per cent suspensions of 18 hour broth cultures of the resistant strain. Other plates were seeded with cultures of the original streptomycin-sensitive strain. Streptomycin solutions (50,000 μg/ml) were placed in the cylinders, and the plates were incubated 18 hours at 37°C. The results reported are from eight experiments performed in quadruplicate.

Plates seeded with the sensitive strain yielded the conventional pattern of clear zones surrounded by areas of good growth except that on media containing 250×10^{-8} moles or more PAS per ml growth outside of the inhibition zones was weak. At a PAS concentration of 1000×10^{-8} moles per ml growth was completely checked and the plates were clear whether streptomycin was present or absent.

On plates seeded with the resistant strain an entirely different pattern obtained. This is shown diagrammatically in figure 1. On control plates (no PAS) there was

[1] J. DUFRENOY and R. PRATT, J. Bact. *53*, 657 (1947). – R. PRATT and J. DUFRENOY, *Antibiotics* (Lippincott, Philadelphia, 1949).

some adverse effect due to streptomycin, but as the concentration of PAS in the medium was increased, the detrimental effect of streptomycin was diminished. When the PAS concentration was increased to levels that inhibited growth (250×10^{-8} moles or more per ml) the effect of streptomycin was reversed and growth of the organisms was enhanced. At the highest concentration of PAS (1000×10^{-8} moles per ml), growth occurred only in a zone immediately around the cylinders from which streptomycin was diffusing.

These results suggest that in this streptomycin-resistant strain of *E. coli* there is an antagonistic relation between PAS and streptomycin and that when the concentration of PAS is sufficiently high to partially or completely block some process essential for growth of the organisms, the resistant strain is able to metabolize streptomycin in such a way as to by-pass the blocked reaction. Results obtained by permitting PAS and streptomycin to diffuse simultaneously from cylinders placed on seeded plates with no PAS in the medium ruled out the possibility that either PAS or streptomycin was chemically inactivated when the two drugs were mixed. The biochemical implications of these observations correlate well with the results published by MASSART[1] to the effect that streptomycin, which by itself does not affect yeast, may relieve the inhibition of respiration caused in that test organism by trypaflavine or other agents. It should be recalled that the effect of streptomycin or of PAS depends markedly on the physico-chemical conditions prevailing in the solutions[2], and notably on the presence of certain cations or anions[3]. Therefore, further interpretation and development of our results may be expected from further research on the relationship between physico-chemical phenomena in solutions of PAS and streptomycin and the responses they elicit in test organisms.

Our results obtained *in vitro* with *Escherichia coli* provide experimental support for the clinical view that PAS therapy should be instituted concomitantly with streptomycin therapy and that combined PAS-streptomycin therapy should never be started after preliminary treatment with streptomycin alone[4]. The same clinical precaution seems to apply to other diseases that are amenable to streptomycin therapy.

We wish to acknowledge the courtesy of the following firms which supplied streptomycin and/or *para*-aminosalicylic acid for this work: Barnes-Hind Laboratories, San Francisco, California; Cutter Laboratories, Berkeley, California; Heyden Chemical Corp., Princeton, New Jersey; Merck and Co., Rahway, New Jersey; Chas. Pfizer and Co., Brooklyn, New York.

KSHITISH J. DIVATIA, GRACE GARDNER, JEAN DUFRENOY, and ROBERTSON PRATT

University of California College of Pharmacy, San Francisco, California, September 30, 1950.

Zusammenfassung

Ein gegen Streptomycin empfindlicher Stamm von *Escherichia coli* kann durch tägliches mehrfaches Überimpfen in eine Nährlösung mit steigendem Gehalt an Antibiotikum gegenüber Streptomycin resistent gemacht werden. Dieser Stamm wächst – wenn genügend Zeit gelassen wird – in einer Lösung, die 300 mg Streptomycin pro Liter enthält. Er zeigt auch normales Wachstum in Agar ohne Streptomycin und im gleichen Medium, das 0 bis 100×10^{-8} Mole *p*-Aminosalizylsäure per cm^3 enthält. Die Bakterien wachsen hingegen nicht bei einer Konzentration von 1000×10^{-8} Mole PAS pro cm^3, wenn nicht Streptomycin hinzugefügt wird. In diesem Fall scheint Streptomycin die wachstumshemmende Wirkung großer PAS-Konzentrationen zu neutralisieren.

[1] L. MASSART, Arch. Intern. Pharmacodynamie *80*, 44 (1949).

[2] J. SOLOMIDÈS, C. r. Soc. Biol. *144*, 105 (1950); Ann. Inst. Pasteur *78*, 602 (1950). – J. SOLOMIDÈS and E. BOURLAND, C. r. Soc. Biol. *143*, 181 (1949).

[3] T. BERTI, Arch. Intern. Pharmacodynamie *82*, 23 (1950).

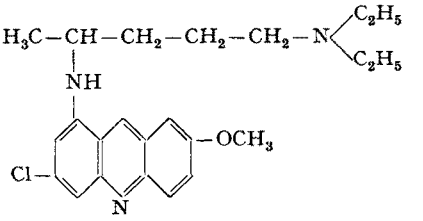
[4] A. DELAUDE, Paris Médical *40*, 458 (1950). – W. J. DILLING, Proc. Roy. Soc. Med. *43*, 53 (1950).

The Colchicine-like Action of an Acridine Derivative

Acridine derivatives have been known as mitotic poisons for many years[1]. In these last years they were investigated chiefly as bacteriostatic and bactericidal substances. Recently we find an important paper of I. LASNITZKI and J. H. WILKINSON[2], who investigated the action of some amino-acridines on the growth of chick fibroblasts: all such acridine derivatives caused disturbance of outgrowth and (or) reduction of mitoses. At the higher concentrations rounding and vacuolisation of nucleoli and vacuolisation of the cytoplasm could be observed. Cells were prevented from entering into division, but there was no interference with the actual process of division, in contrast to colchicine. Therefore abnormal mitoses were not found.

It seemed interesting to study the action on tissue cultures of an acridine derivative that bears a long side-chain and has been already introduced as Atebrin into human therapy, precisely with the aim of preventing the multiplication of an animal cell, the malaria-plasmodium, whose metabolism resembles very closely that of the cells of high vertebrates[3]. It may be important to ascertain whether the long side-chain modifies the cariotropic activity of such compounds in some way.

We used the italian preparation *Italchina* (Farmitalia). Structural formula:



Technique. The cultures were obtained from the cardial region of generally 8–10 days old chick embryos and grown by the hanging-drop technique in a medium consisting of one part chick plasma, one part chick embryo extract, and one part of Tyrode (controls) or Italchina-solution in Tyrode; according to this method (M. I) the acridine derivative acted on the cells during the whole period of growth.

The concentration of the compound definitely acting on growing cells was of course one third of the concentration of the added solution. In some sets of experiments (which are called "M. II" in this paper) we added the Italchina-solution after 24 or more hours of

[1] A. P. DUSTIN, C. r. Soc. Biol. Paris *93*, 465 (1925). – O. BUCHER, Z. Zellforsch. *29*, 283 (1939).

[2] I. LASNITZKI and J. H. WILKINSON, Brit. J. Cancer *2*, 369 (1948).

[3] J. W. MOULDER, Ann. Rev. of microbiol. *2*, 101 (1948).