

consistent, differences were found with other experimental groups, possibly indicating the effects of the deprivation on other systems that are not so important in the behavioral tasks used here. A comparison of the performance of the 8- and 12-day groups on the first and second jump suggests the operation of differential effects of early experience.

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### Synthalin A as Selective Mitotic Poison Acting on $\alpha$ -Cells of the Islets of Langerhans

In recent years it has been discovered that the alpha-cells of the islets of Langerhans, which are considered to be the producers of glucagon (HGF), are seriously affected by synthalin A in adult rats, guinea pigs, and rabbits. Observations on the rabbit have revealed that these cells are at times totally destroyed and that they disappear. Sometimes they are partially destroyed or injured (1-3). This phenomenon is accompanied by a sharp decrease in the blood sugar level. The beta-cells and the exocrine part of the pancreas do not demonstrate any pathological changes.

The action of synthalin A on the alpha-cells of young animals has not been previously studied. Therefore we tested 20 young albino rats (ages ranged from the first to the fifth day of life) by giving each a single subcutaneous injection of decamethylenediguanidinedichlorohydrate in aqueous solution at 10 mg/kg of body weight (4). The animals, including the controls, were sacrificed 12 to 18 hr after injection by decapitation. The abdominal viscera were fixed in Bouin's fluid. Thin paraffin sections were stained by Gomori's chrome-hematoxylin and phloxin method.

The pancreas of normal 1-day-old rats contains well-defined and relatively large

islets of Langerhans. They show the "Mantelinsel"-type, since it is characteristic of the Muridae. The core of beta-cells is surrounded by an incomplete layer of alpha-cells, the covering layer of which often varies in thickness. The beta-cells, especially the granules, in the young and the adult rat are cytologically similar. The granules of the alpha-cells in young animals are coarser and fewer in number in comparison with those in the adult. It was observed that, between the first and fifth days of life, the number of alpha-cells was absolutely and relatively increased through intensive mitotic division. The increase of the beta-cells was substantially smaller. There were many alpha-cell mitoses and few divisions of the beta-cells. The alpha-to-beta relationship changed from 1 to 2.06 on the first day of life to 1 to 1.61 on the fifth day of life. The proportion of alpha-to-beta cells in the adult rat is 1 to 4 or 1 to 5.

After a single subcutaneous injection of synthalin A, the 1-day-old rats did not manifest clinical symptoms. In contrast, the 2- to 5-day-old rats, at a period 12 hr later, exhibited increasing lassitude, shivering, and altered respiration. In none of the young rats treated with synthalin A were the alpha-cells altered; none showed signs of lesions. There were no alterations in granulation, and no hydropic changes or detritus of alpha-cells, which are found in adult rats after treatment with synthalin A.

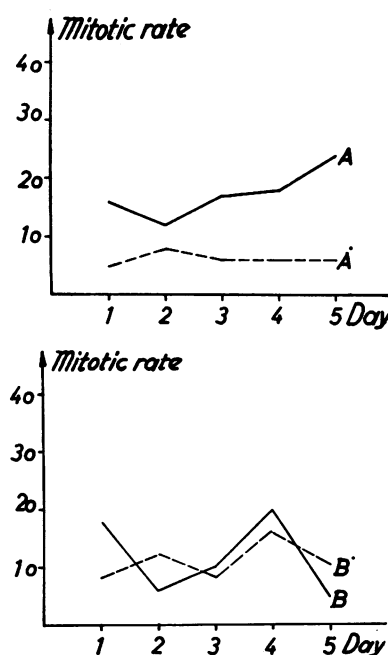


Fig. 1. Above, mitotic rate of alpha-cells in 100 sections through pancreatic islets in rats 1 to 5 days old. (A) controls; (A\*) effect of synthalin A. Below, mitotic rate of beta-cells in 100 sections through pancreatic islets of rats 1 to 5 days old. (B) controls; (B\*) effect of synthalin A.

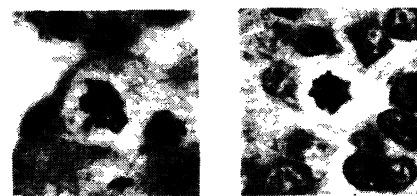


Fig. 2. (Left) Mitotic alpha-cell of 5-day-old rat, control animal,  $\times 700$ . (Right) Mitotic alpha-cell of 4-day-old rat injected with synthalin A (10 mg/kg),  $\times 700$ .

In a comparison of the controls and the treated animals, a notable finding concerning alpha-cell mitosis was made—that is, synthalin-treated rats show a significant decrease in mitotic frequency of the alpha-cells, and the remaining mitotic alpha-cells are injured. In contrast, no mitotic divisions of the beta-cells or of the acinar cells of the pancreas were affected either quantitatively or qualitatively. It is interesting to note that the mitotic rate of the acinar cells was much higher than it was in the alpha-cell layer. The rate of beta-cell mitosis in the synthalin-treated rats was nearly the same as it was in the controls. In the treated animals the frequency of the dividing alpha-cells is decreased to 25 percent of the normal on the fifth day of life. The curve of the mitotic activity rose continually from the second to the fifth day of life in the controls. In injected rats the curve remained on a low level (Fig. 1). Microscopic examination of the mitotic figures of the alpha-cells following synthalin treatment revealed a pycnotic degeneration of the late prophase and early-to-middle metaphase (Fig. 2).

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4. This work has been supported by a grant from the Research Corporation, New York.

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### Thermal Shock and Tooth Decay

In an article by D. G. and H. A. Pohl (1) they state that one of the possible reasons for the increasing incidence of tooth decay is the alternate eating of very hot and cold foods during the same meal. They submit as evidence an experiment in which extracted teeth are subjected to intense thermal shock and then tested by methods that seem to indicate a de-

creased ability to withstand mechanical stress. Hence they feel that structural changes may have occurred decreasing the resistance of teeth to the decaying process.

However, tooth decay is a chemical and not a mechanical process (2). If rapid temperature changes in the mouth alter the tooth structure in any way that should increase the susceptibility to decay, experiments indicating the degree of resistance of thermally shocked teeth to chemical attack should be revealing. Possible approaches to gain such information might be the method of Pigman (3) or the study of the rate of calcium lost from these teeth in solutions of weak acids or chelating agents.

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20 May 1955

We believe that the suggestions of L. S. Vann regarding use of *in vitro* experiments such as leaching or using Pigman's "artificial mouth" technique (1) are excellent. It seems clear that controlled *in vivo* experiments would also be valuable, such as a clear-cut comparison of the caries incidence in white rats subsisting on conventional feed and on a liquid intake of a caries-accelerating fluid only—such as a highly acid fruit juice, or better, a medium rich in free phosphoric acid such as a cola drink (2)—with, say, 50 animals subjected first to severe repeated thermal shocks at their teeth and another 50 held as controls, and a third group of 50 fed like food but only water as liquid intake to serve as background control.

One would expect that within about 6 months of such feeding, differences in caries incidence would be worth examining. Further results, unaccelerated by acid liquid intake, using normal diets and the effect of thermal shock alone, which may require longer times and perhaps larger animal group populations, would of course be even more valuable. If, as a result of such *in vivo* experiments, corroboration is found for the earlier demonstrated indication (3) that thermal shock noticeably affects teeth as determined *in vitro* using extracted teeth, then further work of clinical character would be indicated. Failing such verification, the subject hypotheses should be regarded with much skepticism. The op-

portunity and facilities for so testing the hypothesis are unfortunately not now available to me.

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### Light-Dependence of Fluorescence of Solutions of Cigarette Smoke

For several decades tobacco has been suspected of being a cancer-inducing substance to man. Currently tobacco smoke is being discussed as a cause of the alarming increase of cancer of the human bronchus. In the 1930's Roffo reported the production of cancers in rabbit ears upon the application of tobacco tar (1) and more recently Wynder, Graham, and Croninger have produced cancers in mice following painting of the skin with condensates of cigarette smoke (2).

In the difficult and important search for carcinogens in tobacco smoke, we have studied fluorescence phenomena (3), but a role for 3,4-benzopyrene has not yet been indicated. Roffo and Correa thought they had spectrographic evidence of benzopyrene in tobacco tar (4).

Recent investigations show that highly reactive, radical-forming substances are often carcinogenic (5). Such unstable, easily excited compounds of limited lifetime must be considered in connection with tobacco smoke. The stability of

fluorescence of solutions of tobacco smoke in benzene or petroleum ether was therefore examined (6).

Smoke from a cigarette was passed into a wash bottle containing optically clear benzene, and the effects of light on the fluorescence intensity of the solutions were determined with a Beckman quartz spectrophotometer with excitation at 365 mμ and using a fluorescence standard of 0.1 mg% quinine sulfate in 0.1N H<sub>2</sub>SO<sub>4</sub>.

In daylight, a decrease in fluorescence to 40 percent of the initial level was seen after 1 to 10 days, depending on the light intensity. In the dark, the initial fluorescence remained stable. The decrease noted occurred under oxygen or nitrogen atmospheres, indicating that oxidation is probably not involved. Irradiation with a Hanauer quartz lamp at 30 cm without filter reduced the fluorescence to 10 percent of the initial value in 3 hr. The decrease was irreversible and first order in character; two different time constants were suggested (Fig. 1). Stable and unstable components of the fluorescing material are thus indicated, the latter accounting for 90 percent of the initial fluorescence. Control tests showed that the 6-hr irradiation with the quartz lamp did not affect the fluorescence of the quinine standard or of solutions of pyrene or of 3,4-benzopyrene.

The chemical nature of the indicated unstable compounds is not known, and it is not known whether they are carcinogenic. The possible interest of unstable compounds must be remembered in the search for carcinogens in tobacco smoke, and it is possible that tobacco tars may not preserve the full efficacy of compounds initially present in tobacco smoke.

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6. This work was supported by the Deutsche Forschungsgemeinschaft. A more detailed report of these investigations will be published in the "Arzneimittel-Forschung."

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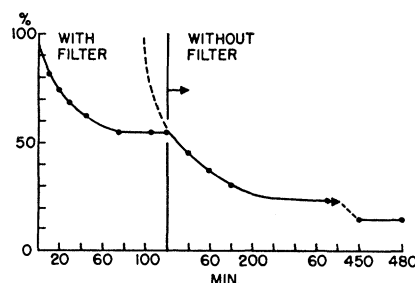


Fig. 1. Decrease of the fluorescence of a solution of cigarette smoke in benzene following irradiation with ultraviolet light. Ordinate: Fluorescence-intensity, in percentage. Abscissa: Time of the ultraviolet irradiation, in minutes (Hanauer-Quartz-Analysenlampe, distance 30 cm).

*Human happiness depends chiefly upon having some object to pursue, and upon the vigor with which our faculties are exerted in the pursuit.*—JOSEPH PRIESTLEY, in the preface to *History of Electricity*.