each six equivalent of Na^+ that move towards the corion (high K^+ leakage) (HUF and WILLS[12]).

Such skin approaches the situation which prevails in nerve, muscle, and red cells in which metabolically coupled ion movements are dominated by a $K^+ \leftrightarrows Na^+$ exchange across the cell membrane (HARRIS[13], HODGKIN and KEYNES[14], KEYNES and ADRIAN[15], MAIZELS[16], SOLOMON[17], STEINBACH[18]).

The frog skin depolarization, which can be obtained under differents conditions, results from an active transport of Na^+ through the skin. We must argue, therefore, that K-Strophantine and K-Strophantoside act with the same mechanism as other drugs. Of course, to maintain the ionic equilibrium, the Na^+ entry must be compensated by an exit of the K^+ through cellular membrane, as occurs in the myocardial cells. Consequently the digitalis drugs act on the frog skin potentials by the same mechanism which works at the level of myocardial tissue. It suggests that this action of digitalis drugs must be fundamentally the same in all parts of the organism.

Hypothetically one might also think that, since the frog skin from the functional point of view is practically like the renal tubulus, the digitalis drugs act directly on the tubular epithelium. The hypothesis that digitalis drugs can act on the diuresis mechanism has always been rejected; on the basis of some recent results, howewer, this hypothesis can be re-accepted (FARBER *et al.*[19]).

It is very difficult, on the basis of our experiments, to confirm such a hypothesis; but we can certainly say that the striking depolarizating actions of the K-Strophantine and K-Strophantoside can be correlated to an exit of the K^+ ions and an active transport of Na^+ ions through the membrane of the epithelial cells of frog skin.

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Résumé

Après une rapide revue de la littérature, les auteurs rendent compte des résultats de leur étude sur l'action dépolarisante de la strophantine K et du strophantoside K sur la peau isolée de la grenouille.

Les résultats démontrent, selon les auteurs, que la strophantine K et le strophantoside K ont la même action sur les potentiels de la peau de la grenouille que sur le myocarde. L'action dépolarisante peut être mise en corrélation avec la sortie des K^+ions et le transport actif des Na^+ ions dans la membrane des cellules épithéliales de la peau de la grenouille.

[12] E. G. HUF and J. P. WILLS, J. gen. Physiol. *36*, 473 (1953).
[13] E. J. HARRIS, Symp. Soc. exp. Biol. *8*, 228 (1954).
[14] A. L. HODGKIN and R. D. KEYNES, J. Physiol. *120*, 46P (1953).
[15] R. D. KEYNES and R. H. ADRIAN, Disc. Faraday Soc. *21*, 265 (1956).
[16] M. LAIZELS, Symp. Soc. exp. Biol. *8*, 202 (1954).
[17] A. K. SOLOMON, J. gen. Physiol. *36*, 57 (1952).
[18] H. B. STEINBACH, Amer. J. Physiol. *167*, 284 (1951); Proc. nat. Acad. Sci., Wash. *38*, 451 (1952).
[19] S. J. FARBER, J. D. ALEXANDER, E. D. PELLEGRINO, and D. P. EARLE, Circulation *4*, 378 (1951).

The Spasmolytic Effect of Patulin

Patulin was first isolated from filtrates of a strain of *Penicillium patulum* Bainier and characterized by BIRKINSHAW *et al.*[1]. The substance has been studied mostly on account of its bacteriostatic effects but pharmacological data are very scanty. The LD_{50} for mice is about 25 mg/kg bodyweight after intravenous administration. AMBACHE has studied the effect of different lactones on the contraction of isolated hamster colon induced by irin[2]. He found that patulin blocked the effect of irin on this preparation.

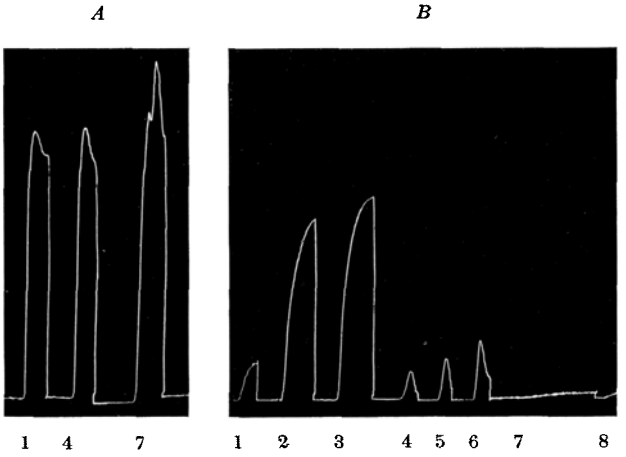


Fig. 1.—Isolated guinea-pig ileum. Bath volume 3 ml.
A Before patulin. *B* With 6·5 μg patulin per ml bath fluid.
Acetylcholine: 1 = 0·075 μg, 2 = 0·15 μg, and 3 = 0·20 μg.
5-HT: 4 = 5 μg, 5 = 10 μg, and 6 = 30 μg.
Prostaglandin: 7 = 0·04 units and 8 = 0·2 units

The modifying effect of patulin on the contractions of isolated guinea-pig ileum induced by different agents was tested in a 3 ml organ bath. The Tyrode solution was kept at 38°C and aerated with oxygen.

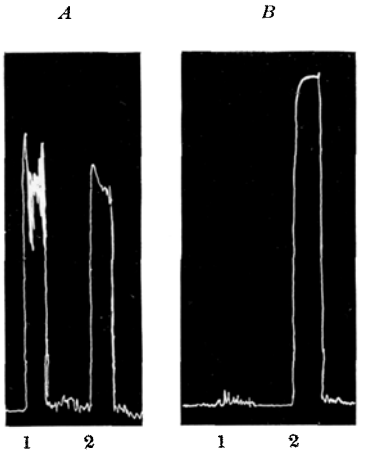


Fig. 2.—Isolated guinea-pig ileum. Bath volume 3 ml.
A Before patulin. *B* With 5 μg patulin per ml bath fluid.
Prostaglandin: 1 = 0·04 units; Substance P: 2 = 2 units

Patulin added to the bath fluid in concentrations of 3–10 μg/ml inhibited the contractions induced by nico-

[1] J. H. BIRKENSHAW, S. E. MICHAEL, A. BRACKEN, and H. RAISTRICK, Lancet *245*, 625 (1943).
[2] N. AMBACHE, J. Physiol. *140*, 24 P (1958).

tine, prostaglandin, pilocarpine, histamine, 5-hydroxytryptamine (5-HT), and acetylcholine (Fig. 1). The substances are mentioned in the order of sensitivity to the inhibition by patulin, nicotine-induced spasm being the most easily inhibited.

Concentrations up to 15 μg patulin/ml bath fluid did not, however, influence the contractions induced by barium chloride or by substance P. The effect of substance P was actually enhanced in most cases (Fig. 2). At concentrations higher than 30 μg/ml bath fluid the effects of barium chloride and substance P were more or less inhibited, but in some cases not completely abolished even after adding 100 μg patulin/ml. The effect of patulin developed slowly and it became almost irreversible.

It seems more or less generally accepted that nicotine gives rise to contraction of the isolated guinea-pig ileum by stimulating the nervous structures of the intestinal wall; that histamine, acetylcholine, and barium chloride stimulate both the nervous structures and the smooth muscle celles directly, and that substance P and prostaglandine (to be published) only stimulate the smooth muscle cells directly. These conclusions have been drawn from experiments which in most cases were based on so-called 'pharmacological histology analyses'.

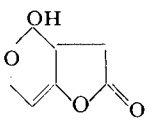
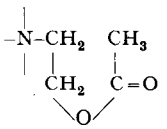


Fig. 3.—Structural formula for patulin.

From the formula given in Figure 3 it is obvious that patulin has chemical similarities with 5-HT, histamine, nicotine, pilocarpine, and acetylcholine, particularly if the acetylcholine molecule is shown in this general form:



The findings in this investigation would seem to suggest that patulin acts as an antimetabolite in some enzymatic reaction by which the substances mentioned above give rise to a contraction of the isolated guinea-pig ileum. Substance P (a polypeptide) and barium chloride (an inorganic compound) would thus seem to activate the contractible system in a different way.

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Zusammenfassung

Patulin verhindert die Kontraktion des isolierten Meerschweinchenileums, verursacht durch Nikotin, Histamin, 5-Hydroxytryptamin, Pilokarpin, Acetylcholin und Prostaglandin. Die Kontraktion, verursacht durch Substanz P und Barium Chloride, wird nicht verhindert.

Numalnarkose und anti-inflammatorische Wirkung von Phenylbutazon

In einer früheren Arbeit (Domenjoz *et al.*[1]) teilten wir mit, dass die am Formalin- und Dextranödem der Ratte erfassbare anti-inflammatorische Wirksamkeit von Natriumsalicylat durch eine gleichzeitige Numalnarkose deutlich abgeschwächt wird. Hingegen liess sich unter identischen Versuchsbedingungen für die Entzündungshemmung durch Phenylbutazon an der Formalinarthritis eine gleichartige Abhängigkeit nicht nachweisen (ohne Narkose: 60% Hemmung; mit Narkose: 64% Hemmung). In der vorliegenden Arbeit wird gezeigt, dass bei Ratten nach mehrtägiger Vorbehandlung mit Schilddrüsenextrakt bzw. Thyroxin ein starker Verlust des antiphlogistischen Wirkungsgrades des Phenylbutazon eintritt, wenn die Tiere gleichzeitig mit Numal (Diäthylaminsalz der Isopropylallylbarbitursäure) narkotisiert wurden.

Antiphlogistische Wirkung von Phenylbutazon 200 mg/kg subkutan am Formalinödem mit Schilddrüsenextrakt bzw. Thyroxin vorbehandelter Ratten mit und ohne Numalnarkose.

K = Kontrollen Ph = Phenylbutazon

Mit Narkose				Ohne Narkose			
Tierzahl	Tiergewicht g	Schwellung in mm³	Hemmung in %	Tierzahl	Tiergewicht g	Schwellung in mm³	Hemmung in %
Schilddrüsenextrakt							
K 20	152	276	—	26	146	250	—
Ph 25	145	197	29	27	148	77	69
Thyroxin							
K 27	134	332	—	20	126	203	—
Ph 26	133	336	1	9	126	72	65

Methodik. Der Entzündungsversuch erfolgte nach der Methode von Domenjoz *et al.*[1]. Als entzündliches Agens injizierten wir männlichen, weissen Ratten 0,1 cm³ Formalin 3%ig subplantar in die linke Hinterpfote. Phenylbutazon (Butazolidin Geigy) wurde in einer Dosis von 200 mg/kg subkutan 30 min vor Formalin verabreicht. Als Narkotikum applizierten wir Numal (W. Z. Roche) in einer Dosierung von 100 mg/kg subkutan 45 min vor Injektion des Phenylbutazon. Die Ödemintensität erfassten wir 135 min nach der Formalinverabreichung.

Die Tiere wurden vorbehandelt mit Schilddrüsenextrakt 7 Tage täglich 500 mg/kg per os (Thyreo-Mack; 1 Tablette = 0,1 g *glandula thyreoidea sicca*, entsprechend 0,5 g frischer Schilddrüse) bzw. Thyroxin 8 Tage täglich 2,5 mg/kg subkutan.

Der Entzündungsversuch erfolgte 24 h nach der letzten Substanzverabreichung.

Ergebnisse. In der Tabelle sind die Resultate der Ödemmessung zusammengestellt.

Die antiphlogistische Wirkungsintensität von 200 mg/kg Phenylbutazon subkutan an der Formalinarthritis der Ratte erfährt keine Abnahme durch Numalnarkose (Domenjoz *et al.*[1]) oder mehrtägige Vorbehandlung der

[1] R. Domenjoz, K. Mörsdorf, E. G. Stenger und W. Theobald, Arch. exp. Path. Pharmak. *230*, 325 (1957).