of incubation (80% hydrolysis). Some leaflets jut out from its surface. The adjacent leaflets apparently were cleaved off by exposure to the venom. No attempt was made to correlate the extent of hydrolysis with the electron microscopic appearance of the spherulites. It was apparent, however, that intact spherulites rarely were seen in the hydrolysate.

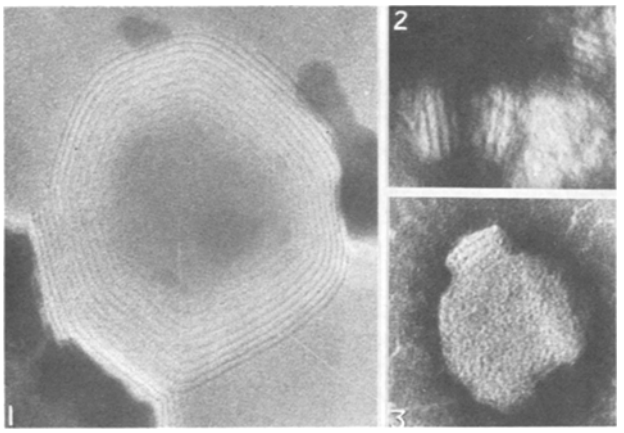

Fig. 1. Lecithin spherulite before exposure to phospholipase A. × 250,000.

Fig. 2. Stacks of bimolecular leaflets from a lecithin solution which had been hydrolyzed for 2 min. × 250,000.

Fig. 3. Lecithin spherulite after hydrolysis for 110 min. × 250,000.

It was expected that phospholipase A would disrupt the bilaminar aggregates of lecithin through the in situ generation of lysolecithin as based on the observations of BANGHAM and HORNE[2]. The results of the present study are consistent with their observations and further indicate that hydrolysis of lecithin by phospholipase A, under some conditions, is accompanied by cleavage of stacks of lamellae from the spherulite.

Zusammenfassung. Durch Phospholipase A des Giftes von *Pseudechis porphyriacus* spalten sich während der Lecithin-Hydrolyse Lamellenstapel von der Oberfläche der Phospholipidspheruliten ab.

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The Mechanism of Blood Vessel Permeability Derangement Under the Influence of Histamine, Serotonin and Bradykinin

Electron microscopic studies have shown[1] that under the influence of inflammatory agents or permeability factors (histamine, serotonin etc.) partial separation of endothelial cells occurs, thus increasing vessel permeability. To explain this phenomenon it was supposed that endothelial cells have contractile structure that contracts under the influence of permeability factors[2,3]. The shortlasting increase of vessel permeability under the conditions described[4] is in favour of this view. If permeability increase is the result of active contractility of cell structure, it must be an energy-requiring process. To verify this point of view, the effects of histamine, bradykinin and serotonin on vessels were studied, tissue respiration being suppressed by cyanide.

In the first series of experiments on rabbits, guinea-pigs and Wistar rats, solutions of NaCN (0.1 ml) (10^{-2} to $10^{-4}M$) in 0.1 *M Tris* HCl-buffer (pH 7.4) were introduced i.c. into shaved parts of the flanks. Then 0.1 ml solutions of bradykinin (0.5 µg)[5], histamine (10 µg) or serotonin (0.5 µg) were introduced into the same parts of skin with different intervals.

In control experiments the mediators were introduced into the parts of skin with *Tris* HCl-buffer previously injected. The injection of NaCN solutions served as an additional control. 20 tests were made on each rabbit, 10 on each guinea-pig and 8 on each rat. Immediately after the s.c. injections, Evans blue solution (20 mg/kg) was administered i.v. to test vessel permeability.

In all cases of control experiments, the mediators increased skin vessel permeability (the diameter of blueing exceeds 9 mm). Cyanide did not cause the derangement of permeability and circulation (the measurements of skin temperature). In the experiments on rabbits, $10^{-2}M$ NaCN fully and $10^{-3}M$ NaCN solutions partially inhibited the responses of vessels to histamine and bradykinin. The most pronounced inhibition occured 10–15 min after cyanide injections (Table).

In guinea-pigs and rats the effects[1] of cyanide were also significant, though somewhat less pronounced than in rabbits. $10^{-2}M$ NaCN solution significantly inhibited the influence of serotonin on rat skin vessels. Analyzing the data described above it is necessary to take into account that the true cyanide concentration in skin was lower than that administered, due to cyanide transfer into circulation.

In the second series the influence of cyanide on the development of vessel permeability derangement was studied on rat mesentery. NaCN (10^{-2}–$10^{-3}M$) solutions in *Tris* HCl-buffer in a volume of 0.1 ml were dropped on the part of the mesentery. In 3 min Indian ink (0.08 ml/100 g) was introduced i.v. and in 2 more min 0.1 ml of bradykinin (1 µg), histamine (5 µg) or serotonin (20 µg) was applied to the parts of mesentery affected by cyanide. In control experiments, mediators were used

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[5] Synthetic bradykinin BRS 640 was obtained through the courtesy of Dr. K. NEFF and Dr. B. LARSONNEUR, Sandoz AG, Basel.

after *Tris* HCl-buffer. In all the cases of control experiments, a pronounced increase of venule permeability occured that was seen from the blackening of the vessel walls. $10^{-2}M$ NaCN solution almost fully suppressed the responses of vessels to mediators used. The inhibition was significant though less pronounced in the experiments with $10^{-3}M$ NaCN. The application of cyanide solutions used on the mesentery did not cause any visible disturbances of microcirculation.

In the third series of experiments, the influence of cyanide on the development of rat leg oedema was studied. $10^{-2}M$ NaCN solution in *Tris* HCl-buffer in a volume of 0.1 ml was injected into the hind leg plantar surface. For control, 0.1 ml *Tris* HCl-buffer was introduced into the second hind leg 10 min later. 0.1 ml solution of histamine (10–25 μg), bradykinin (25 μg) or serotonin (25 μg) was injected into the leg with NaCN previously applied. Into the second leg 0.1 ml of saline was introduced. 60 min after that, the intensity of oedema was measured by weighing the amputated legs. Cyanide fully inhibited plantar oedema induced by histamine and bradykinin and weakened the serotonin oedema by 50%.

The influence of NaCN on the development of rabbit skin vessel permeability derangement caused by bradykinin and histamine

NaCN solutions	Time after NaCN administration (min)			
	5	10	15	30
Bradykinin				
$10^{-2}M$	2/8	0/8	1/8	1/8
$10^{-3}M$	1/8	1/8	3/8	6/8
$10^{-4}M$	7/8	8/8	8/8	8/8
Histamine				
$10^{-2}M$	1/8	0/8	0/8	1/8
$10^{-3}M$	2/13	0/13	1/13	6/13
$10^{-4}M$	10/12	6/12	9/12	10/12

The numerator is the number of tests without permeability derangement. The denominator is the total number of tests.

The results of the present experiments confirm the supposition of the active and energy-requiring character of the endothelial membrane permeability enhancement under the influence of permeability factors. In the following experiments we have investigated the possibility of inhibiting by cyanide vessel response to usual inflammatory agents. The rabbits were first injected s.c. with 0.1 ml $10^{-2}M$ NaCN solution in *Tris* HCl-buffer, 10 min later Evans blue solution was given i.v. Simultaneously the parts of skin injected with cyanide were painted with 0.02 ml of xylene. In other experiments inflammation was produced on the parts of skin with cyanide by applying to it for 1 min a copper disc 15 mm in diameter maintained by circulating water at a temperature 54 ± 0.5 °C. In control experiments xylene and heat were applied to the parts of skin with *Tris* HCl-buffer previously injected. In these experiments vessel permeability derangement has proved to be practically identical. Consequently, the inhibitory effect of cyanide was not detected. The results of these experiments show the complexity of the mechanisms of blood vessel permeability derangement in inflammation. Mediators seem to play a relatively unimportant part in this process in comparison with other mechanisms (direct injury and others) independent of aerobic tissue respiration.

Выводы. Опытами с воздействием гистамина, брадикинина и серотонина на сосуды кожи кроликов, морских свинок и крыс, как и на сосуды брыжейки и лапы крыс показано, что предварительное местное применение 10^{-2}–10^{-3} M NaCN тормозит возникновение нарушений проницаемости венул. В отличие от этого цианид не тормозит возникновение повышения проницаемости сосудов кожи кролика и брыжейки крысы под влиянием воспалительных агентов (ожог, ксилол). Результаты опытов свидетельствуют против доминирующей роли факторов проницаемости в патогенезе повышения проницаемости сосудов при воспалении.

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Influence de la vagotomie chez la tanche *Tinca tinca* au cours d'une surcharge pluricationique (eau de mer diluée). Variation des cations Na^+, K^+, Ca^{++} et de l'intensité de la respiration tissulaire

La section des nerfs parasympathiques est suivie d'effets variables chez les Téléostéens: chez une espèce euryhaline, l'Anguille, la vagotomie n'altère pas la possibilité d'osmorégulation de l'espèce[1]. En particulier, le rapport Na/K dans les tissus et les excreta, n'est pas modifié chez les animaux opérés. Par contre, les influences hormonales sont importantes; ainsi CHAN et al.[2] ont noté une diminution de ce rapport chez les Anguilles hypophysectomisées. Chez une espèce sténohaline, la Tanche, nos expériences ont mis en évidence, chez les vagotomisées, une augmentation de 50% du rapport Na/K dans les tissus hépatiques et une diminution du même ordre de grandeur dans les excreta[3–4]. Lorsqu'on soumet les Poissons à une surcharge sodique en les maintenant dans une solution de ClNa à 12‰, ces troubles s'aggravent par rétention sodique. Il était intéressant de connaître le comportement de cette espèce à la suite d'une surcharge saline comprenant plusieurs cations, conditions réalisées dans l'eau de mer.

Pour cela nous avons utilisé une eau de mer synthétique diluée environ au tiers, ce qui correspond à 13 g de sels par l[5]. Comme dans nos expériences précédentes, un lot homogène de Tanches témoins et vagotomisées sont placées dans des aquariums de 10 l où l'eau aérée et filtrée est progressivement amenée à la concentration désirée.

Les animaux sont ensuite soit sacrifiés pour la mesure de l'intensité respiratoire, ou des cations Na^+, K^+, Ca^{++} du tissu hépatique, soit placés individuellement dans 4 l

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[4] J. PÉQUIGNOT et A. SERFATY, Experientia *24*, 567 (1968).
[5] Eau de mer synthétique réalisée à partir de sels «Tropic-Marin-Neu» (44 éléments) (Western Germany).