that the thymidine-rich chain of satellite DNA is associated with the DNA chain of the same polarity in each pair of telocentric chromosomes which fuse. Since this arrangement was observed for nine different metacentric chromosomes, involving 15 of the 19 autosomes, it is likely that this is the general rule for centric fusion in the mouse.

The published data for the association of telocentric into metacentric chromosomes in the mouse allow the construction of a "chain" of centric fusions which links 18 of the 19 autosomes (*6, 10*). (No centric fusion with chromosome number 18 was reported.) For example, chromosome 15 has been observed to fuse with chromosomes 5 and 6, which have been observed to fuse with chromosomes 4 and 19. If it is assumed, as suggested above, that the thymidine-rich chain of satellite DNA is associated with the DNA chain of the same polarity in every pair of telocentric chromosomes that fuse to form a metacentric chromosome, then these results suggest that the thymidine-rich chain of satellite DNA is associated with the same DNA chain (in terms of polarity) in every mouse autosome. This finding may be relevant to the evolution of the chromosome complement in the mouse.

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References and Notes

1. M. S. Lin, S. A. Latt, R. L. Davidson, *Exp. Cell Res.* **86**, 392 (1974).
2. S. A. Latt, *Proc. Natl. Acad. Sci. U.S.A.* **70**, 3395 (1973).
3. I. Hilwig and A. Gropp, *Exp. Cell Res.* **75**, 122 (1972).
4. W. G. Flamm, M. McCallum, P. M. B. Walker, *Proc. Natl. Acad. Sci. U.S.A.* **57**, 1729 (1967).
5. A. Gropp, U. Tettenborn, E. von Lehmann, *Cytogenetics* **9**, 9 (1970).
6. B. J. White, J.-H. Tjio, L. C. Van de Water, C. Crandall, *Proc. Natl. Acad. Sci. U.S.A.* **69**, 2757 (1972).
7. J. G. Brewen and W. J. Peacock, *ibid.* **62**, 389 (1969).
8. R. Kavenoff and B. Zimm, *Chromosoma* **41**, 1 (1973).
9. S. A. Latt, R. L. Davidson, M. S. Lin, P. S. Gerald, *Exp. Cell Res.*, in press.
10. A. Gropp, H. Winking, L. Zech, H. Muller, *Chromosoma* **39**, 265 (1972); L. Zech, E. P. Evans, C. E. Ford, A. Gropp, *Exp. Cell Res.* **70**, 263 (1972).
11. Supported by NIH grants HD04807 and HD06276. We thank Drs. Samuel A. Latt and Park S. Gerald for suggestions and Dr. Latt for the use of his fluorescence microscope. We also thank Dr. Alfred Gropp for the tobacco mice, Dr. Beverly White for the 36T mice, and Dr. H. Loewe for the 33258 Hoechst.

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Pulmonary Alveolar Hypoxia: Release of Prostaglandins and Other Humoral Mediators

Abstract. *Hypoxic ventilation of isolated perfused cat lungs caused the frequent appearance in pulmonary perfusates of biologically active substances, which included prostaglandins or prostaglandin-like compounds. In anesthetized cats, inhibition of prostaglandin biosynthesis with infusions of aspirin (more than 50 milligrams per kilogram) reduced the pulmonary vasoconstrictor and bronchoconstrictor responses to hypoxic breathing.*

It has long been recognized that hypoxia induces constriction of pulmonary vessels, but the mechanisms of this reaction have remained incompletely understood (*1*). Recent evidence has suggested the possibility that the pulmonary vascular response to hypoxia may be mediated by chemical substances released from the lung. Such evidence includes: (i) the presence of lung tissue is required for the pressor response; pulmonary vessels stripped of lung tissue fail to constrict when exposed to low Po_2 (*2*); (ii) hypoxic pulmonary hypertension is reduced or abolished by cooling (*3*); and (iii) hypoxic ventilation is accompanied by morphologic signs of secretory activity in certain cells of the lung (*4*). We now report that alveolar hypoxia may provoke the synthesis and release of prostaglandin-like compounds and other mediators from isolated cat lungs, and that inhibition of prostaglandin biosynthesis in intact cats reduces the pulmonary vasoconstrictor and bronchoconstrictor responses to hypoxia.

We used two experimental approaches. (i) We perfused isolated cat lungs, allowing the perfusate from the lung to superfuse isolated smooth-muscle organs, for continuous detection and assay of any released biologically active material. (ii) We assessed the effect of metabolic inhibition of prostaglandin (PG) biosynthesis on the pulmonary vascular (and airway) reactions to hypoxia in the intact cat.

Perfusion of isolated cat lungs was carried out in 32 experiments. The lungs were perfused in situ (*5*) with 5 percent dextran in Krebs solution (19 experiments) or with a 1 : 1 mixture of this solution with the cat's own blood (13 experiments). The perfusing fluid was prewarmed to 37°C and pumped at a constant flow rate of 10 ml/min. Pulmonary venous pressure was maintained at 3 mm-Hg, and the outgoing perfusate constantly superfused (*6*) a series of up to four isolated smooth-muscle organs, selected from: trachea, ileum, and gallbladder of guinea pig; stomach and colon of rat; and chick rectum. The specificity of the responses of isolated organs was enhanced by pretreating them, in 22 instances, with agents which blocked the effects of histamine, serotonin, catecholamines, and acetylcholine (a solution containing 10^{-7} g of mepyramine maleate per milliliter, 2×10^{-7} g of methysergide bimaleate per milliliter, 2×10^{-6} g of propranolol HCl per milliliter, 10^{-7} g of phenoxybenzamine HCl per milliliter, and 10^{-7} g of hyoscine HBr per milliliter). The tissue responses were measured with Harvard isotonic transducers and continually recorded by a Beckman Dynograph. Perfusion (pulmonary arterial) pressure also was continually recorded. Samples of outflow perfusate also were collected during the experiment for subsequent assay and confirmation of the "on line" results. The lungs were ventilated with 21 percent O_2, 5 percent CO_2 in N_2, or with 2 percent O_2, 5 percent CO_2 in N_2, at predicted normal tidal volume and frequency. Hypoxic breathing was maintained for at least 10 minutes, and was repeated after the vascular and isolated tissue responses had returned to control range, or had stabilized at new levels.

A pressor response (mean pulmonary arterial pressure increase of at least 1 mm-Hg) was observed during hypoxia in 24 of the 32 experiments and averaged 31.6 percent for Krebs-dextran perfusions, or 38.7 percent for perfusions where blood was added. Whenever pulmonary hypertension occurred, it was accompanied by contraction of one or more of the assay organs (Fig. 1) in all but four cases. The contractions were independent of the presence of blood in the perfusate, and occurred in the following percentages of times in which the respective tissue was used: guinea pig trachea, 71; guinea pig gallbladder, 54; rat stomach strip, 38; rat colon, 31; guinea pig ileum, 29; chick rectum, 19. In 21 of these 24 experiments, the responses

Table 1. Change in pulmonary vascular resistance (mm-Hg liter^{-1} min^{-1}) during hypoxic breathing (26 experiments, six cats).

	Control			After aspirin (> 50 mg/kg)		
	Air	8.7% O_2	Increase (%)	Air	8.7% O_2	Increase (%)
Mean	19.9	27.9	40.2*	22.8	27.2	19.3*
S.E.	2.8	2.8	11.3	1.3	1.3	4.6
P	< .01			< .0125		

* The difference in these two values is significant at the level $P < .0025$.

were unaffected by the addition of blockers of histamine, serotonin, α- and β-adrenergic, and cholinergic receptors.

Since the P_{CO_2} and pH of the perfusate were unchanged, because of constant inspired P_{CO_2} and ventilation, and since the mere lowering of P_{O_2} of the superfusing solution did not cause any tissue contraction and actually decreased resting tone (*7*), the contractions of assay organs must have been due to biologically active substances appearing in the perfusate. The contraction of guinea pig ileum, rat stomach strip, and chick rectum suggested the appearance in the perfusate of PGE-like compounds, with the activity of up to 50 ng of PGE_2 per milliliter. The contraction of rat colon and guinea pig trachea suggested the presence of PGF-like compounds, with the activity of up to 50 ng of $PGF_{2\alpha}$ per milliliter. Some of the organ responses, especially gallbladder contraction, could not be attributed solely to PG's. In only 3 of the 24 experiments associated with pulmonary arterial pressure rise were the tissue responses decreased or abolished by the pharmacologic blockers listed above. The blocked responses were: contraction of guinea pig ileum and gallbladder in one case, suggesting the presence of histamine, and contraction of ileum alone in two cases, suggesting the presence of serotonin.

A second group of experiments was conducted to confirm the release of PG's during hypoxic ventilation and to evaluate their contribution to pulmonary hypertension. The experimental approach was based on the premises that: (i) PG release is a consequence of stimulated PG synthesis, rather than their discharge from preexistent stores (*8*), and (ii) aspirin can inhibit PG biosynthesis, and thus also their release (*9*).

Six anesthetized cats (pentobarbital) weighing 3 to 4.5 kg, were ventilated by a Harvard pump with either room air or 8.7 percent O_2 in N_2, at constant tidal volume and frequency. Pressures in the pulmonary artery and left atrium were measured by transducers connected to catheters placed in those chambers, and cardiac output (minus coronary flow), was recorded by means of an electromagnetic flowprobe (Carolina Medical Electronics, Inc.), placed around the ascending aorta. Pulmonary vascular resistance (PVR), a measure of several factors including pulmonary vascular response (*10*), was calculated as the difference between mean pulmonary arterial and left atrial pressure, divided by cardiac output. Tracheal pressure was monitored and, at constant tidal volume, provided a measure of airway smooth-muscle responses. Alveolar hypoxia was maintained for 5-minute intervals, repeated 15 minutes after return to air breathing. A saline solution of aspirin (6 mg/ml) was infused intravenously, over approximately 30 minutes, in a total dose of 50 mg/kg. After the completion of the infusion, hypoxic breathing was repeated. Arterial blood P_{O_2}, P_{CO_2}, and pH did not change significantly following the administration of aspirin. During alveolar hypoxia, PVR increased 40.2 percent (Table 1), but the increase was limited to 19.3 percent after aspirin ($P < .00025$). Simultaneously, tracheal pressure increased by 8.9 ± 2.8 percent during hypoxia before aspirin, and increased only 2.1 ± 3 percent after aspirin ($P < .05$).

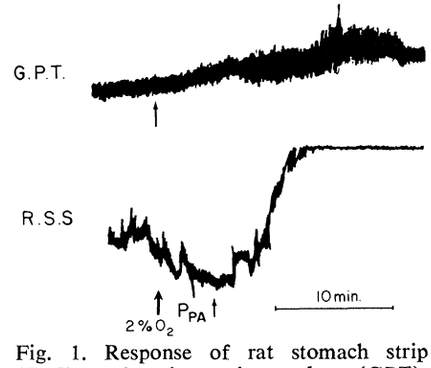

Fig. 1. Response of rat stomach strip (*RSS*) and guinea pig trachea (*GPT*), superfused with perfusate of isolated lung. Ventilation with 2 percent O_2 was begun at the first arrow. Upward movement signifies contraction of smooth-muscle organs, which had been rendered insensitive to histamine, serotonin, catecholamines, and acetylcholine. Perfusion (pulmonary arterial) pressure (P_{PA}), recorded separately, rose at the second arrow.

The attenuation of the vascular and airway responses to hypoxia following the administration of aspirin (*11*) is additional suggestive evidence of PG release during hypoxia, and of the contribution of this release to the pressor and bronchoconstrictor reactions. PGF compounds, for example, $PGF_{2\alpha}$, are potent constrictors of pulmonary vessels, as well as of airway smooth muscle (*12*). Additional possible mechanisms for the protective effect of aspirin include its inhibitory action on platelet aggregation (*13*), also related to suppression of PG synthesis, and a nonspecific decrease in the responsiveness of the pulmonary vessels.

If it is established that hypoxia provokes pulmonary synthesis and release of PG's, this response would be opposite to that of at least some systemic tissues and organs, where oxygen lack may inhibit PG synthesis (*7*). The release of PG's from the lung during alveolar hypoxia would also provide another example of the possible participation of these compounds in the pathogenesis of pulmonary lesions. PG release has already been reported in anaphylaxis (*14*), pulmonary embolism (*14*), and hyperventilation (*15*).

The failure in some of our perfusion experiments, as well as in experiments by others (*14*), to demonstrate evidence of PG-like activity in the perfusate might have been due to the inactivation of these agents by the lung (*16*), before they reached the intravascular space. The evidence, on occasion, for the presence of histamine and of serotonin supports the conclusions of earlier workers using pharmacologic antagonists (*17*) and morphologic (*4*) and histochemical techniques (*4*). Additional mediators, for example, angiotensin II, and as-yet-unidentified lung peptides (*18*), might have been released during hypoxia, but their identification by bioassay, in the presence of prostaglandins, could not be ascertained.

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References and Notes

1. E. H. Bergofsky, F. Haas, R. Porcelli, *Fed. Proc.* **27**, 1420 (1968); Y. Enson, C. Giuntini, M. L. Lewis, T. Q. Morris, M. I. Ferrer, R. M. Harvey, *J. Clin. Invest.* **43**, 1146 (1964).
2. T. C. Lloyd, Jr., *J. Appl. Physiol.* **25**, 560 (1968).
3. A. Hauge, *Prog. Respir. Res.* **5**, 145 (1969).
4. F. Haas and E. H. Bergofsky, *J. Clin. Invest.* **51**, 3154 (1972); J. M. Lauweryns and M. Cokelaere, *Z. Zellforsch.* **145**, 421 (1973); *Experientia* **29**, 1384 (1973).
5. J. B. Glazier and J. F. Murray, *J. Clin. Invest.* **50**, 2550 (1971).
6. J. R. Vane, *Br. J. Pharmacol.* **35**, 209 (1969).
7. A. Eckenfels and J. R. Vane, *ibid.* **45**, 451 (1972).
8. J. R. Weeks, *Ann. Rev. Pharmacol.* **12**, 317 (1972).
9. J. R. Vane, *Nat. New Biol.* **231**, 232 (1971).
10. R. M. Harvey and Y. Enson, *Adv. Intern. Med.* **15**, 73 (1969).
11. In preliminary experiments with Dr. N. Hara, small doses of indomethacin (1 to 10 mg/kg) did not prevent the hypoxic pressor response, and sometimes even enhanced it. Larger doses (100 mg/kg), however, appeared to reduce the hypoxic pulmonary hypertension.
12. P. J. Kadowitz, P. D. Joiner, A. L. Hyman, *Proc. Soc. Exp. Biol. Med.* **145**, 53 (1974); A. P. Smith, in *The Prostaglandins*, P. W. Ramwell, Ed. (Plenum, New York, 1973), vol. 1, p. 203.
13. M. B. Zucker and J. Peterson, *Proc. Soc. Exp. Biol. Med.* **127**, 547 (1968).
14. P. J. Piper and J. R. Vane, *Ann. N.Y. Acad. Sci.* **180**, 363 (1971).
15. S. I. Said, *Fed. Proc.* **32**, 1972 (1973).
16. P. J. Piper, J. R. Vane, J. H. Wyllie, *Nature (Lond.)* **225**, 600 (1970).
17. A. Hauge, *Circ. Res.* **22**, 371 (1969); ——— and N. C. Staub, *J. Appl. Physiol.* **26**, 693 (1969).
18. S. I. Said, S. Kitamura, V. Mutt, in *Chemistry and Biology of Peptides*, J. Meienhofer, Ed. (Ann Arbor Science, Ann Arbor, Mich., 1972), p. 409.

19. Supported by Pulmonary Center (SCOR) award HL-14187 from the National Heart and Lung Institute, NIH. We thank Wallace T. Ford, Jr., Linda Ward, Richard Schmitt, and Hyacinth Deon for skillful assistance.

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Nuclear Waste Disposal in the Oceans

In their article "Disposal of nuclear wastes" (*1*) Kubo and Rose give an excellent updated assessment and discussion of many of the problems of disposing of radioactive wastes from nuclear fission reactors. They note that today no proved, operational long-term storage facility for high-level wastes is available. They find, however, several attractive technological options that have been given little consideration, and they conclude that the following options appear to be either usable or worth further exploration: mausoleums; disposal in mines, and perhaps in ice; in situ melt; and further chemical separations. They state, furthermore, that it is too early to assess disposal in space.

Kubo and Rose, however, appear to deal too lightly with disposal in the oceans as an option that is worth further exploration. They dispense with this option by noting that it "seemed unsafe for lack of adequate knowledge about all the consequences of failure—a situation that still obtains." The idea of dumping large amounts of high-level nuclear wastes into the oceans has in the past been met with strong opposition because of the unknown risks involved. International agreement would, furthermore, be required before such a program which had met certain criteria of safety could be implemented. Still, the potential of the oceans as dumping ground for the high-level nuclear wastes from fission reactors (after chemical removal and nuclear burning of the actinides) is very attractive. Petros'yants (*2*) summarized the situation thus in 1972 (referring to the risks connected with disposal of nuclear wastes in the oceans): "The fears are unquestionably founded, and therefore it is essential, in the interest of protecting the seas and oceans from radioactive contamination, to conduct a series of extremely serious scientific studies before making the decision to utilize this method of disposal of solid radioactive wastes in the depths of the oceans. . . . The disposal of wastes in the ocean at depths of 5000 m and more is extremely attractive, but it is essential, of course, to make absolutely certain that this is a reliable and safe approach, and that radioactivity will not be scattered throughout the oceans. Such solutions will apparently be found: it is too attractive to use the enormous ocean expanses for the purposes."

One approach to disposal of high-level nuclear wastes in the oceans emphasizes the concept of containing the solidified wastes in containers for a period of approximately 700 years, which is sufficient for the fission products to have decayed to safe levels. It would probably be more expedient to rely instead on the low leach rate of the glasses employed to solidify the nuclear wastes, under the environmental conditions prevailing at the ocean floor. The individual glass bodies in free contact with seawater could then be made sufficiently small (of the size of tennis balls) so that the heat and radiation generated by the nuclear wastes would not disintegrate the glass bodies by cleavage or crystallization. Suitable glasses that have leach rates ten times smaller than that of common bottle glass (at a pressure of 1 atm) are already known. Such low leach rates appear to be compatible with safe disposal of solidified high-level nuclear wastes after removal of the actinides (*3*).

The option of disposal of high-level nuclear wastes in the oceans does not appear to have received the attention it deserves. More work on this option and international cooperation are called for if we, who live in the western part of the world, want to assure ourselves that nuclear power is going to resolve our energy needs in the coming decades. We cannot afford to neglect such a relatively inexpensive option as long as we do not have an operational long-term storage facility for high-level wastes. Besides, some countries, of which Denmark may be an example, might have difficulty demonstrating, in time for the final disposal of their accumulated nuclear wastes in mausoleums, and to the satisfaction of their people and the international community, that they possess underground geological formations that are suited for safe disposal of high-level nuclear wastes.

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References

1. A. S. Kubo and D. J. Rose, *Science* **182**, 1205 (1973).
2. A. M. Petros'yants, *From Scientific Research to the Atomic Industry* (JPRS-60584, Joint Publication Research Service, Washington, D.C., 1973), p. 180; translated from *Ot Nauchnogo Poiska k Atomnoy Promyshlennosti* (Atomisdat, Moscow, ed. 2, 1972).
3. W. F. Merritt, in *Disposal of Radioactive Wastes into the Ground* (International Atomic Energy Agency, Vienna, 1967), p. 403.

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Since he wrote his comment, Nielsen and one of us have met in Cambridge, Massachusetts, to discuss the issue. We agree that a key to the issue is better separation of the waste components. After that, several hitherto nonoptions become at least conceivable, and perhaps possible. Ocean disposal is one of these.

As we emphasized in our article, high-level nuclear wastes fall into two general categories: (i) fission products, with half-lives of 30 years or less, which are for all practical purposes benign after 700 years; and (ii) the actinides, with half-lives of typically 25,000 years or more, whose hazard persists into geologic time. The two categories can be separated in the waste reprocessing plant, much more com-