3) The hypothesis we favor is that this imitation is based on the neonate's capacity to represent visually and proprioceptively perceived information in a form common to both modalities. The infant could thus compare the sensory information from his own unseen motor behavior to a "supramodal" representation of the visually perceived gesture and construct the match required (*7*). In brief, we hypothesize that the imitative responses observed are not innately organized and "released," but are accomplished through an active matching process and mediated by an abstract representational system. Our recent observations of facial imitation in six newborns—one only 60 minutes old—suggest to us that the ability to use intermodal equivalences is an innate ability of humans. If this is so, we must revise our current conceptions of infancy, which hold that such a capacity is the product of many months of postnatal development. The ability to act on the basis of an abstract representation of a perceptually absent stimulus becomes the starting point for psychological development in infancy and not its culmination.

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References and Notes

1. For example, J. Piaget, *Play, Dreams and Imitation in Childhood* (Norton, New York, 1962); H. Werner and B. Kaplan, *Symbol Formation* (Wiley, New York, 1963); I. Uzgiris and J. Hunt, *Assessment in Infancy* (Univ. of Illinois Press, Chicago, 1975). See D. Parton [*Child Dev.* 47, 14 (1976)] for a recent review of the literature concerning infant imitation. Some reports are in conflict with these age norms. In the most extensive of these, O. Maratos [thesis, University of Geneva (1973)] noted imitation of two facial gestures by 1- to 2½-month-old infants. However, the interpretation of her work is limited by the fact that the three factors discussed in the text were not controlled.
2. In addition, the following procedural details were held constant for both experiments. All infants were full term (40 ± 2 weeks gestation), of normal birth weight (3400 ± 900 g), and born through an uncomplicated vaginal delivery with a minimum of maternal medication (for example, no general anesthesia). The infants were tested when awake and alert, and they were supported in a semiupright posture by a well-padded infant seat. All the gestures were silently demonstrated 35 cm from the infant's eyes. They were presented against a white cotton backdrop and illuminated by a 20-watt spotlight placed directly above and behind the infant's head. The experimental room was kept as free as possible from auditory distraction and was maintained in subdued, indirect lighting.
3. S. Siegel, *Nonparametric Statistics* (McGraw-Hill, New York, 1956).
4. There was no significant difference ($P > .05$) between the duration of the presentation of the tongue protrusion ($\bar{X}$ = 67.6 seconds) and mouth opening ($\bar{X}$ = 74.8 seconds) gestures. Preliminary work revealed that infants continued to make sucking movements for about 3 seconds after a pacifier was removed. Therefore, in all cases, a 3-second interval was timed after the pacifier was removed and before the beginning of the 150-second baseline or response period. The infant's oral activity during this interval was not included in the analyses.
5. A tongue protrusion was scored only when the tongue was thrust clearly beyond the lips. A mouth opening was tallied only when the infant fully opened his mouth. Intraobserver agreement (number of agreements divided by the total number of agreements plus disagreements) was high for both tongue protrusion (93 percent) and mouth opening (92 percent).
6. K. Lorenz and N. Tinbergen, *Z. Tierpsychol.* 2, 1 (1938); N. Tinbergen, *A Study of Instinct* (Oxford Univ. Press, New York, 1951).
7. "Supramodal" is used, following T. Bower [*Development in Infancy* (Freeman, San Francisco, 1974)], to denote that the representation is not particular to one sensory modality alone.
8. A preliminary version of parts of experiment 1 was presented at the Biennial Meeting of the Society for Research in Child Development Denver, Colo., 10 to 13 April 1975. Portions of this research were reported in A.N.M.'s thesis [Oxford University (1976)]. Supported by NSF grant GS42926, the Social Science Research Council, the Washington Association for Retarded Citizens, and the Child Development and Mental Retardation Center of the University of Washington (grant HD02274). This research has greatly benefited from the encouragement and advice provided by Drs. J. S. Bruner and G. P. Sackett. We thank Drs. D. Holm, S. Landesman-Dwyer, O. Maratos, D. Gentner, and P. Kuhl for helpful suggestions. We are especially indebted to M. DurkanJones for her long and careful work on this project. We also thank W. Barclay, D. Blasius, J. Churcher, D. Clark, A. Gopnik, V. Hanson, R. Hart, M. McCarry, G. Mitchell, and V. Papaioannou. We acknowledge the cooperation of University Hospital of the University of Washington.

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Transplantable Pancreatic Carcinoma of the Rat

Abstract. *Pancreatic carcinoma, which developed in a male Fischer 344 rat fed 0.1 percent nafenopin for 20 months, is being successfully transplanted into weanling rats. The tumor cells contain variable numbers of zymogen granules, and the endoplasmic reticulum and the Golgi apparatus appear prominent. This transplantable tumor, which displays substantial amylase and lipase activity, should serve as a useful model system for immuno- and chemotherapeutic experiments, as well as for the study of synthesis, storage, and release of zymogen proteins in neoplastic cells.*

Epidemiological studies indicate an unequivocal increase in the incidence of pancreatic carcinoma in several countries during the past three decades (*1*, *2*). In the United States, pancreatic carcinoma ranks as the fourth most common cause of death by cancer, exceeded only by cancer of the lung, large bowel, and breast (*2*). Difficulty in early diagnosis, as well as lack of adequate knowledge of its biological behavior, appear to be major factors contributing to the poor prognosis of pancreatic carcinoma in humans (*3*). Since several studies suggest that pancreatic cancer in man may be etiologically related to exogenous chemicals and thus preventable (*4*), attempts are being made to develop suitable animal models of this cancer (*5*) which could serve as an effective system for various experimental manipulations aimed at preventing or altering the natural progression of the disease. Here we describe a transplantable pancreatic carcinoma of the rat which is capable of producing amylase and lipase.

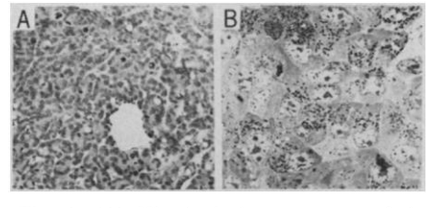
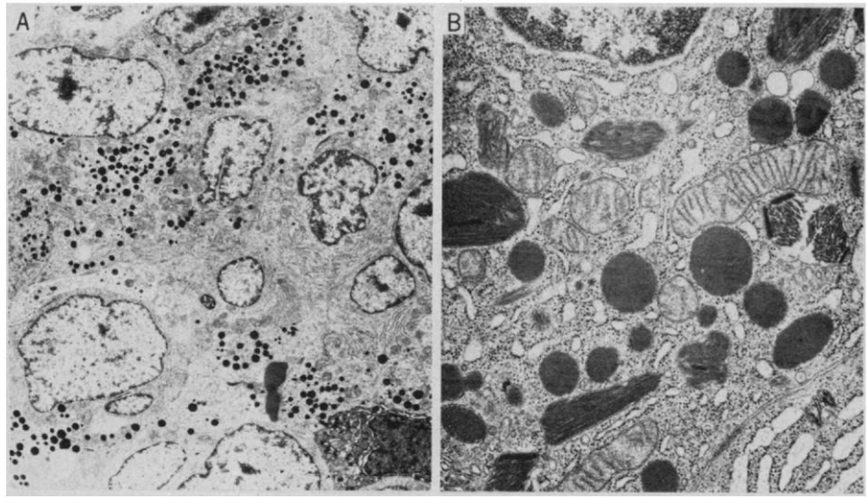


Fig. 1. (A) Histological appearance of the original pancreatic carcinoma from a male Fischer 344 rat treated with nafenopin for 20 months. Acinar differentiation is evident, and numerous mitoses are present. (Hematoxylin and eosin; ×80.) (B) Subcutaneous transplant of pancreatic carcinoma (second generation), fixed in 2.5 percent glutaraldehyde in 0.1*M* cacodylate buffer, *p*H 7.4, for 30 minutes and then in 1 percent OsO_4. This section (0.5 μm thick) of plastic-embedded tissue shows numerous secretory granules in the cytoplasm of tumor cells. (Toluidine blue; ×450.)

The primary tumor developed in the pancreas of a male Fischer 344 rat that was fed nafenopin (2-methyl-2-[*p*-(1, 2, 3, 4-tetrahydro-1-naphthyl)phenoxy]propionic acid; Su-13437), at a dietary concentration of 0.1 percent for 20 months. Nafenopin is a potent hepatic peroxisome proliferator (*6*) and, as reported elsewhere (*7*), the majority of rats fed this compound develop liver tumors. The primary pancreatic tumor was highly vascular, measured 6 cm in diameter, and contained several cystic spaces filled with straw-colored fluid. Metastases were present in the liver. Histologically, the tumor was a well-to-poorly differentiated pancreatic acinar carcinoma originating from exocrine tissue (Fig. 1A). On electron microscopic examination, the primary pancreatic carcinoma cells revealed large nuclei with prominent nucleoli; the cytoplasm displayed abundant rough endoplasmic reticulum and prominent Golgi apparatus. Numerous zymogen granules were also seen in the tumor cells. Portions of this primary tumor were minced and diluted in sterile normal saline for inoculation into the peritoneal cavity at laparotomy,



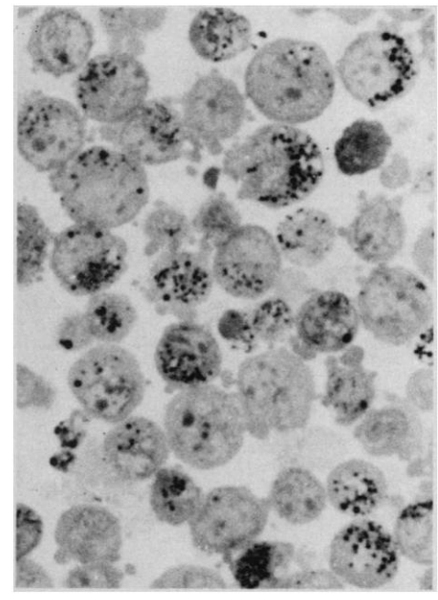


Fig. 2 (left). (A) Electron microscopic appearance of a subcutaneous transplant of pancreatic carcinoma (third generation). Rough endoplasmic reticulum and zymogen granules are prominent. (×2000) (B) Fourth generation subcutaneous transplant. Ribosomes and endoplasmic reticulum are prominent. Some zymogen granules are pleomorphic and consist of fibrillar material. Tissue fixed in glutaraldehyde and OsO_4 as in Fig. 1B. (×11000) Fig. 3 (right). Light micrograph of dissociated tumor cells from the fifth generation transplantable pancreatic carcinoma. The section (0.5 μm thick) of Epon-embedded, partially washed cells was stained with toluidine blue. The tumor cells are generally spherical and many contain zymogen granules. (×780)

into five male weanling Fischer 344 rats weighing 50 to 80 g. Subsequent transplantations were performed in weanling rats either intraperitoneally, or subcutaneously in the inguinal region.

The primary transplants became palpable within 6 weeks. The size of these tumor transplants increased progressively thereafter, causing abdominal distension and peritoneal hemorrhage. The subcutaneously transplanted tumors, from second generation onward, usually became palpable within 3 weeks. The animals with subcutaneously transplanted tumors survived 3 to 5 months, whereas rats bearing intraperitoneally transplanted tumors died within 3 months. Histologically, the tumor remained moderately to poorly differentiated throughout the first five generations. Zymogen granules were observed in tumor cells (Fig. 1B) of both subcutaneous and intraperitoneal tumor transplants. At the ultrastructural level, the rough endoplasmic reticulum and the Golgi apparatus appeared prominent; no significant difference in the subcellular differentiation between subcutaneous and intraperitoneal tumor transplants was noted. The number of zymogen granules varied somewhat in tumor cells (Fig. 2, A and B). When these tumors were less than 1 cm in diameter, that is, during the initial growth period, the tumor cells contained an occasional zymogen granule. Tumors larger than 2 cm in diameter were very vascular and contained cystic spaces filled with fluid rich in amylase and lipase activity. The number of tumor cells containing zymogen granules appeared to increase with tumor size. Zymogen granules were seen in tumor cells throughout the first five transplant generations. Irregular bundles of microfilaments were also present in the cytoplasm of many cells. The apical junctional complex between adjacent tumor cells resulted in the formation of a lumen revealing projections of microvilli. Other junctional complexes such as desmosomes were also present. Currently, the tumor is in its sixth transplant generation.

This transplantable pancreatic carcinoma is easily dissociable into individual cells by enzymatic digestion, divalent cation chelation, and gentle shearing (*8*). A relatively homogeneous, viable, and functionally active tumor cell population can be obtained (Fig. 3). The dispersed pancreatic carcinoma cells, though spherical, appear to retain the polarized distribution of zymogen granules in the cytoplasm.

The serum lipase as well as amylase activity increased substantially in rats bearing transplantable pancreatic carcinoma. (The serum amylase activity in tumor-bearing rats was 25300 ± 4200 units per 100 ml, whereas the control value was 863 ± 61 units per 100 ml; lipase activity in tumor-bearing rats was 6610 ± 840 units per 100 ml, whereas the control value was 100 ± 10 units per 100 ml.) Homogenates of the pancreatic carcinoma displayed approximately one-third of the amylase and lipase activity of the normal pancreas (*9*).

The transplantable pancreatic carcinoma described here may provide a useful model for immunotherapy and chemotherapy experiments. Although the majority of pancreatic carcinomas in man are believed to be of ductal origin (*10*), this transplantable tumor may yield some worthwhile information about the biological properties of pancreatic carcinoma in general. In addition, this tumor will be useful in investigating the synthesis and transport of zymogen proteins (*11*) in neoplastic cells, and in elucidating the mechanisms of hormonal action on pancreatic acinar cell function

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References and Notes

1. R. Doll, C. S. Muir, J. A. H. Waterhouse, *Cancer Incidence in Five Continents* (Union Internationale Contre le Cancer, Monogr. No. 2, Geneva, 1970); E. L. Wynder, *Cancer Res.* **35**, 2228 (1975).
2. National Cancer Institute, Biometry Branch, *The Third National Cancer Survey Advanced Three Year Report 1969–1971 (excluding carcinoma in situ)* (National Institutes of Health, DHEW Publ., (NIH) 74-637, Bethesda, Md., February 1974). It is estimated that each year over 20,000 new cases of cancer of the pancreas are diagnosed in the United States and approximately 19,000 individuals with this cancer die. The age adjusted mortality increased from 2.9 to 8.2 per 100,000 population from 1920 to 1965 [L. S. Krain, *Digestion* **6**, 356 (1972)] and if this trend continues it can be estimated that the current rate will double by the year 2000 [R. A. Pledger, R. R. Bates, U. Saffiotti, *Cancer Res.* **35**, 2226 (1975)].
3. J. S. Macdonald, L. Widerlite, P. S. Schein, *J. Natl. Cancer Inst.* **56**, 1093 (1976); P. J. Fitzgerald, *Arch. Pathol. Lab. Med.* **100**, 513 (1976); I. Cohn, *Cancer* **37**, 582 (1976); S. M. Baylor and J. W. Berg, *J. Surg. Oncol.* **5**, 335 (1973). Pancreatic cancer is rarely diagnosed at an early stage because of the nonspecific nature of the initial symptoms. By the time physical signs are demonstrable, the tumor is generally inoperable because of extensive local invasion and metastatic spread; 5-year survival rate is less than 5 percent.

4. E. L. Wynder, K. Mabuchi, N. Maruchi, *J. Natl. Cancer Inst.* **50**, 645 (1973); D. L. Levin and R. R. Connelly, *Cancer* **31**, 1231 (1973).
5. R. J. Elkort, A. H. Handler, P. J. Mozden, *Int. J. Cancer* **16**, 810 (1975); D. S. Longnecker and T. J. Curphey, *Cancer Res.* **35**, 2249 (1975); P. Pour, J. Althoff, F. Krüger, D. Schmahl, U. Mohr, *Cancer Lett.* **1**, 3 (1975); P. Pour, F. W. Krüger, J. Althoff, A. Cardesa, U. Mohr, *Cancer Res.* **35**, 2259 (1975); J. K. Reddy and M. S. Rao, *ibid.*, p. 2269; J. Dissin, L. R. Mills, D. L. Mainz, P. D. Webster, *J. Natl. Cancer Inst.* **55**, 857 (1975); R. T. Jones, L. A. Barrett, C. Van-Haaften, C. C. Harris, B. F. Trump, *ibid.* **58**, 557 (1977).
6. J. K. Reddy and T. P. Krishnakantha, *Science* **190**, 787 (1975); J. K. Reddy, D. L. Azarnoff, D. J. Svoboda, J. D. Prasad, *J. Cell Biol.* **61**, 344 (1974).
7. J. K. Reddy and M. S. Rao, *J. Natl. Cancer Inst.* in press.
8. The procedure of dissociation is a modification of the technique of A. Amsterdam and J. D. Jamieson [*J. Cell Biol.* **63**, 1037 (1974)]. When injected subcutaneously, these dissociated tumor cells gave rise to palpable tumor masses in 3 to 4 weeks.
9. Determinations of serum amylase and lipase were made according to the methods of W. T. Caraway [*Am. J. Clin. Pathol.* **32**, 97 (1959)] and J. H. Roe and R. E. Byler [*Analyt. Biochem.* **6**, 451 (1963)], respectively. For the determinations of amylase and lipase in pancreas and transplantable tumor, homogenates were prepared in 0.1*M* phosphate buffer, *p*H 7.0. The homogenates were sonicated for 1 minute under ice, and centrifuged under refrigeration at 14000 rev/min (Beckman J21C) for 20 minutes. The supernatants were assayed for the enzyme activity.
10. A. L. Cubilla and P. J. Fitzgerald, *Cancer Res.* **35**, 2234 (1975). Pancreatic carcinomas are classified according to their supposed origin from ductal or acinar epithelium. Acinar cell carcinoma of the pancreas may account for about 10 percent of all pancreatic carcinomas [J. N. Webb, *J. Clin. Pathol.* **30**, 103 (1977)]. The incidence may be much higher since a number of pancreatic carcinomas classified as anaplastic or undifferentiated may indeed represent poorly differentiated tumors of acinar cell origin.
11. G. Palade, *Science* **189**, 347 (1975); S. S. Rothman, *ibid.* **190**, 745 (1975); J. P. Kraehenbuhl, L. Racine, J. D. Jamieson, *J. Cell Biol.* **72**, 406 (1977).
12. Supported by grants GM 23750 and N01-CP-75876 from the Public Health Service. We thank D. G. Scarpelli and D. S. Longnecker for comments on the manuscript.

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Hypertension and the Nature of Stress

Friedman and Iwai (*1*) showed that psychic stress can produce some degree of hypertension in rats. This effect was shown in rats that give a strong hypertensive reaction to excessive salt ingestion but not in rats that were not selected for this characteristic. Friedman and Iwai conclude that "there is still insufficient evidence to allow attributing to stress a primary etiological role in essential hypertension."

The failure of Friedman and Iwai to produce hypertension in unselected rats agrees with other studies in which electrical shock or other unpleasant physical stimuli were used as stressors; in these studies it proved difficult to demonstrate marked lasting changes in blood pressure (*2*). Other studies, however, have demonstrated lasting and clear changes in blood pressure after exposure to stress. How do the studies that show such changes differ from those which do not? It appears that the nature of the stressor is important. If the experimental animals are confronted with conspecifics (*3*) or species enemies (*4*) in agonistic encounters, marked and lasting hypertensive reactions can be shown. Such reactions may be highly specific, as suggested by the opposing responses of the iliac artery of a cat confronted with another cat or a dog (*5*). In some species, local vascular responses to agonistic encounters with conspecifics can be extremely strong. Tree shrews, for instance, may die of uremia after repeated exposure to such encounters; the uremia was presumably caused by severe and lasting constriction of the renal arteries (*6*).

Different stressors are probably not equally effective in activating the mechanism underlying hypertension. One dimension along which stressors can differ is in the type and intensity of emotional reactions they produce (*7*). It may be argued that as far as the experimental production of hypertension through psychic stress is concerned, stress imposed by physical means, such as electrical shock, is less effective in eliciting strong appropriate emotional reactions than stress imposed through encounters with species enemies or conspecifics. Thus, in establishing an animal model of hypertension produced by psychic stress it may prove useful to take into account the differential sensitivity of mechanisms underlying hypertension to stressors differing in nature.

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References

1. R. Friedman and J. Iwai, *Science* **193**, 161 (1976).
2. H. J. Benson, J. A. Morse, W. H. Kelleher, *Am. J. Physiol.* **29**, 408 (1967); R. P. Forsyth and R. E. Harris, *Circ. Res. Suppl.* **26**, 13 (1970); M. Gruner and S. Nitschkoff, *Acta Biol. Med. Ger.* **24**, 595 (1970).
3. J. P. Henry, J. P. Mehan, P. M. Stephens, *Psychosom. Med.* **29**, 408 (1967).
4. J. Schunk, *Z. Klin. Med.* **152**, 251 (1954).
5. G. Baccelli, G. D. Ellison, G. Mancia, A. Zanchetti, *Experientia* **27**, 1183 (1971).
6. D. von Holst, *J. Comp. Physiol.* **78**, 236 (1972).
7. J. P. Henry, *Geriatrics* **30**, 59 (1976).

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Peters suggests that the nature of the stressor is the crucial variable in the development of stress-induced blood pressure elevations. On the basis of our research, we concur that this is an important factor to consider when assessing the etiological significance of stress in the pathogenesis of hypertension. We had demonstrated that the simple application of electrical shocks or severe food deprivation did not produce hypertension in salt-sensitive rats (*1*). However, placing these rats in a conflict situation in which responses resulted in electrical shocks and food deprivation did elevate the blood pressure. These specially bred rats have exhibited blood pressure sensitivity to a variety of putative hypertensinogenic stimuli. It is now appropriate to list psychological stress, that is, conflict, among them. The elevations in blood pressure we obtained using conflict were much less pronounced and persistent than those obtained using other stimuli (*2*). It is possible that exposing these rats to other types of stress which presumably affect the higher portions of the central nervous system, such as confrontation with conspecifics or species enemies, would result in hypertension as severe as that observed upon exposure to a high-salt diet or renal artery constriction. However, we maintain that until such a demonstration has been reported, there still is insufficient evidence to attribute to stress a primary etiological role in essential hypertension.

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References

1. R. Friedman and L. K. Dahl, *Psychosom. Med.* **37**, 402 (1975).
2. L. K. Dahl, K. D. Knudsen, J. Iwai, J. P. Rapp, D. Jaffe, in *Hypertension 1972*, J. Genest and E. Koiw, Eds. (Springer-Verlag, Berlin, 1972), pp. 337–349; R. Friedman and J. Iwai, *Proc. Soc. Exp. Biol. Med.* **155**, 449 (1977); R. Friedman and L. K. Dahl, in *Stress and the Heart*, D. Wheatley, Ed. (Raven, New York, 1977), pp. 137–156.

11 August 1977