and serum histaminase should both be determined in additional cases of medullary thyroid carcinoma; the flare response should be studied during the third trimester of pregnancy, when circulating histaminase activity is high; and it would be of interest to determine whether administration of aminoguanidine, a potent inhibitor of histaminase, would restore the response in cases of medullary carcinoma.

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HORMONAL CONTRACEPTIVES AND FIBROADENOMAS OF BREAST

To the Editor: The conclusions of Wiegenstein et al. (N Engl J Med 284:676, 1971) regarding the association of oral hormonal contraceptive agents and adenofibromas seem inappropriate. They noted that 12 of 67 women with adenofibromas had multiple lesions, and that 11 of the 12 reportedly received hormonal contraceptives. It should be noted that all these lesions were excised during the "oral contraceptive era," and that no mention is made of the number of the remaining 55 women receiving such medications.

In 1961 we described 79 women who had had adenofibromas excised before the introduction of oral hormonal contraceptives.[1] Fifteen of these women had multiple adenofibromas, resulting in an incidence almost identical to that reported by Wiegenstein et al.

In their letter, as well as in their recent article,[2] the authors imply an association between hormonal contraceptives and florid epithelial hyperplasia in adenofibromas. Intraductal epithelial proliferation of variable degree was seen in 22 per cent of patients in our series, and some of these lesions manifested a "florid" pattern of growth. Similarly, Fechner was unable to identify any distinctive morphologic pattern in adenofibromas removed from women taking oral contraceptives.[3] As he noted, the widespread use of oral contraceptives and the frequency of tumors such as adenofibromas may account for their random coincident occurrence in the same patient, and yet cannot be taken as proof of a causal relation.

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CONTRACEPTION AND PULMONARY EMBOLISM

To the Editor: In the recent report by Zimmerman, Adelson and Ratnoff entitled "Pulmonary Embolism and Unexpected Death in Supposedly Normal Persons," (N Engl J Med 283:1504-1505, 1970) a statistical chi-square test led the authors to conclude "that the effect of oral contraceptive therapy on the frequency of pulmonary embolism is not dramatic." This conclusion was incorrectly inferred for two reasons: the chi-square test is inappropriate for testing population incidences when the frequency is very small (the correct distribution is the Poisson); correct statistical methodology requires more than "significance tests."

Consider first the death rates for men and nonpregnant women. The Poisson distribution indicates a difference that is significant at the 15 per cent level. This differs markedly from the chi-square test.

Consider next the difference between nonpregnant women in two time periods. If, indeed, an attempt is being made to measure the possible influence of oral contraceptives, there is now an underlying assumption that women in period 2 were users whereas women in period 1 were not. But the data do not assure us on this point: of the 10 deaths occurring in period 2, only one of the women is known to have been using contraceptive pills, and nothing is known about the other nine women. This fact alone casts doubt on any test involving these data.

The most disturbing aspect of the previous researchers' report is their conclusion. Their purpose was "to determine the effect of the introduction of oral contraceptive agents . . ." Their data neither indict nor clear oral contraceptives. (This is contrary to the findings of the British and FDA Committees.)

Furthermore, the "traditional" significance levels in cases of this kind may easily lead to improper decisions on the part of physicians and patients. A conclusion based on sampling technics, because of an "unusual sample," can be wrong in two ways: a Type I error is made if on the basis of the evidence oral contraceptives are impugned when in fact they are innocent of increasing the death rate; a Type II error is made if oral contraceptives are "cleared" when in fact they increase the death rate. In making a judgment, one must view the costs of Type I and Type II errors. Oral contraceptives are often used by healthy subjects with adequate alternatives. Thus, the cost of a Type I error may be largely inconvenience. The cost of a Type II error, on the other hand, may require the unanticipated ultimate payment. The severe cost attached to Type II errors usually dictates that the traditional significance level be altered.

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To the Editor: The article by Zimmerman et al. in the December 31, 1970, issue of the *Journal* concerning unexpected, fatal, autopsy-confirmed pulmonary embolism in normal persons adds useful information to the body of population-based statistics on this cause of death.[1] Tabulations of such events are not ordinarily recorded in published vital-statistics reports and permit assessment of changes in rates of relatively uncommon diseases that might be attributed to the introduction of new environmental agents such as oral contraceptives.

On the basis of the data of these investigators, certain interesting comparisons with the published literature on thromboembolic complications of oral contraceptives may be made. It has been estimated that the risk of death from this cause is increased eight times[2] by these drugs and that morbidity is increased three to six times.[3-5]

The authors observed an increase in mortality rate from 3.04 to 3.96 per 1,000,000 in nonpregnant females; during the same period, the rate in males decreased. Assuming that 15 per cent of the population was using oral contraceptives,[6] the increase in rate observed in females is consistent with a fourfold increase in risk attributable to oral contraceptive use.

The number of cases was small, and, consequently, tests of significance are negative (regardless of whether one uses expected values derived from the null hypothesis of no additional risk for women using the oral contraceptives or the alternative hypothesis of an increase of several times in risk for such women) and are not helpful in the interpretation of these data.

However, this analysis does indicate the close agreement of these data with those previously published; the authors' conclusion that the impact of the oral contraceptives is "not dramatic" thus may be misleading.

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5. Sartwell PE, et al: Thromboembolism and oral contraceptives: an epidemiological case-control study. Am J Epidemiol 90:365-380, 1969
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The above letters were referred to the authors of the article in question, one of whom offers the following reply:

To the Editor: Dr. Kassouf objects to the use of the chi-square test to determine whether a significant increase in the incidence of deaths from pulmonary embolism occurred during the years 1962-1969 as compared to 1951-1962. Dr. Arthur S. Littell, now of the University of Texas at Houston, our statistical consultant, disagrees and confirms that no significant increase occurred in deaths in nonpregnant women in the second period. Dr. Kassouf further suggests that the cost of a Type I error – impugning oral contraceptives when in fact they are innocent of increasing the death rate – may be largely inconvenience. He makes the assumption that the alternative to the pill is a safer form of contraception. Although this may be true for some segments of the population, in others the alternative is an unwanted pregnancy, carrying with it the risks of parturition or abortion. On this basis, the safety of the pill is indeed a pertinent question.

Drs. Schrogie and Seigel suggest that our data are not inconsistent with a substantial increase in risk from pulmonary embolism attributable to oral contraceptive use, not made clearly apparent from overall statistics. Dr. Littell and I agree. As we pointed out, however, a review of all fatal cases of pulmonary embolism at University Hospitals of Cleveland during the years 1962-1969 did not reveal a single case in a patient without serious underlying disease. If pulmonary embolism has increased in this area, it is not striking from our studies. I believe that our original conclusion, that the data presented suggest that the effect of oral contraceptive therapy on the frequency of pulmonary embolism in Cuyahoga County is not dramatic, is correct.

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PARADOXICAL CEREBRAL AIR EMBOLISM

To the Editor: A man with a central-venous-pressure catheter died here recently after paradoxical air embolism to the brain via a patent foramen ovale. This case demonstrates a hazard of central-venous-pressure catheters not mentioned in previous reports in the *Journal*.[1-4]

Our patient was a 61-year-old man recovering from vagotomy and pyloroplasty for a benign gastric ulcer. One week after surgery, during ambulation, his No. 14 central venous catheter separated from the administration tubing, allowing air into the venous system. He collapsed almost immediately but was supported, avoiding the trauma of a fall. Although the vital signs remained stable throughout the initial course, coma, with diffuse neurologic impairment and seizures, rapidly developed. Three days later he died of cardiac arrest. Post-mortem examination revealed a large patent foramen ovale, with congestive heart failure. The brain demonstrated multiple and diffuse areas of recent white-matter demyelinization and infarction, without any sign of vascular occlusion.

This case illustrates a mechanism for neurologic damage after venous air embolization. Deaths from that cause have previously been reported and have been explained by froth in the ventricle[5] or fibrin blockade of the pulmonary capillary bed,[6] but we have seen no reports of immediate neurologic lesions after the introduction of air through a central venous catheter. The studies of Emerson et al.[7] demonstrated that air does not pass through the pulmonary circulation into the systemic circuit. In our case, the large patent foramen ovale and the widespread neurologic damage are consistent with a paradoxical air embolus to the brain.

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SELECTIVE IgA DEFICIENCY AND AUTOIMMUNITY

To the Editor: A recent clinicopathological exercise in the *Journal*[1] presents new evidence for an association between the thymus, IgA deficiency, cancer, autoimmune disease and recurrent infection. The case described was that of a 70-year-old woman with a thymoma, selective IgA deficiency, pernicious anemia and recurrent pulmonary infections. This combination of abnormalities is not likely to be fortuitous. IgA deficiency is known to be associated with thymic abnormalities in ataxia-telangiectasia, in which an increased prevalence of infection and autoimmune phenomena has been observed.[2] In the Wiskott-Aldrich syndrome there are elevated IgA and thymic abnormalities.[3] The association of the thymus and IgA has also been demonstrated experimentally. In certain thymectomized animals IgA deficiency develops[4,5] and autoimmunity and cancer are known to be more frequent.[6]

The difficult problem in patients with selective IgA deficiency is the determination of the basic defect. Does selective IgA deficiency occur first and then lead to an attrition of thymic function and loss of cell-mediated immunity, with subsequent autoimmune disease or cancer? The evidence suggests that selective IgA deficiency is a congenital defect and that cell-mediated immunity is normal in most cases.[7] If a thymic defect is present, it is sufficiently subtle so that it cannot be determined by current laboratory methods. The case in the *Journal* suggests that the thymoma was a development late in life, as was the appearance of cell-mediated immunity deficiency. It would be of interest to know whether the patient showed depletion of thymic-dependent areas of lymphoid tissue.

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