admission, and a computerized axial tomographic scan of the head performed on October 12 revealed a large area of infarction in the right frontoparietal area. After the scan, the patient became oliguric and increasingly obtunded. Serial renal-function tests revealed a progressive rise in the serum creatinine concentration to a maximum of 11 mg per deciliter. Physical examination gave no evidence of volume depletion as judged by the presence of normal skin turgor, the absence of an orthostatic drop in blood pressure and neck veins that were not flat. The urinalysis revealed a specific gravity of 1.011, with a 1+ test for protein and no granular casts or renal tubular epithelial cells in the sediment. No known nephrotoxins had been administered other than the 100 ml of methylglucamine diatrozoate (Renografin 60 per cent), used to enhance the scan. The patient's subsequent hospital course was one of stabilization followed by spontaneous diuresis and a rapid return of renal function to its previous level.

In the absence of any other possible cause of this transient exacerbation of renal failure, we propose that it was due to the contrast medium used to "enhance" the tomographic scan. This type of reaction has been well described in diabetic patients with renal failure,[1-3] and one large study[2] has indicated that the frequency may approach 100 per cent in diabetic patients with a base-line creatinine greater than 4.5 mg per deciliter. Furthermore, it may not be appreciated that a computerized tomographic scan of the head is routinely performed with enhancement in some centers unless otherwise requested. This procedure may expose many patients with chronic renal failure, with or without diabetes mellitus, to the risk of further renal impairment, which may at times be irreversible.[1]

MICHAEL R. THEERMAN, M.D.
ALLEN SHUSTER, M.D.
JAMES E. FANALE, M.D.
Worcester, MA 01605 Memorial Hospital

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PROLACTIN LEVELS IN TARDIVE DYSKINESIA

To the Editor: The neurochemical lesion in tardive dyskinesia is unknown. One hypothesis suggests that there may be an imbalance between dopaminergic and cholinergic neurons in the basal ganglions.[1] Owing to the chronic blockade of dopamine receptors caused by neuroleptic drugs, these receptors may become hypersensitive[1] or increased in number.[2] Prolactin secretion is under dopaminergic control; prolactin has been used as a marker to demonstrate dopamine excess in patients with Huntington's chorea.[3,4] However, attempts to show enhanced prolactin suppression in response to dopamine agonists in patients with tardive dyskinesia have been unsuccessful.[5] We examined the prolactin response to stimulation with thyrotropin-releasing factor in four schizophrenic patients (age range of 33 to 64 years, with a mean of 46 years) with tardive dyskinesia (Table 1).

Table 1. Prolactin Response to 500 μg of Thyrotropin-Releasing Factor.

CASE NO.	PROLACTIN RESPONSE*				
	0 TIME	AT 30 MIN	AT 60 MIN	AT 90 MIN	AT 120 MIN
1	10	110	80	48	32
2	14	64	38	34	24
3	32	142	84	48	38
4	14	64	30	10	16

*Normal basal prolactin level is ≤20 ng/ml. Response to thyrotropin-releasing factor usually exceeds 300%.

The response was normal in all four patients, suggesting that prolactin secretion may not reflect central dopaminergic hypersensitivity or that this hypersensitivity may not exist in tardive dyskinesia. However, this study was limited because psychiatric considerations made it impossible to withdraw neuroleptic drugs completely before testing with thyrotropin-releasing factor. In addition, the diagnosis of tardive dyskinesia is made solely on clinical grounds and probably encompasses a heterogeneous population. Studies in centers following larger groups of patients may define a subset with impaired prolactin responsiveness and, perhaps, a more uniform response to drug therapy.

KENNETH L. COHEN, M.D.
RICHARD A. COOPER, M.D.
SUSAN ALTSHUL, M.S.N.
West Haven Veterans Administration
West Haven, CT 06516 Hospital

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STREPTOKINASE/STREPTODORNASE FOR SKIN TESTING

To the Editor: We have identified an easily correctable problem associated with streptokinase/streptodornase intradermal skin testing. Streptokinase/streptodornase preparations are used regularly to assess the potential for delayed hypersensitivity responsiveness in clinical settings, often as a "control" during routine skin testing with purified protein derivative of tuberculin. When the preparations are so used, the recommended dose for intradermal injection is 5 IU per 0.1 ml — 4 units of streptokinase and 1 unit of streptodornase.[1] Recently, we observed three cases of an accentuated delayed hypersensitivity reaction manifested by a markedly indurated (80-mm), erythematous and painful area at the injection site, accompanied by fever (maximum temperature of 38.3°C). Investigation revealed that these patients received streptokinase/streptodornase prepared on the ward from bottles labeled "Streptokinase/Streptodornase Varidase for Intramuscular Use. Not for Intravenous Use." When this material was diluted as recommended in the package insert, the concentration was 1000 IU per 0.1 ml. This final concentration is 200 times greater than appropriate for skin testing, but is that recommended for use "in the treatment of edema associated with trauma or infection."[2] This error occurred because the hospital pharmacy was requested to supply "streptokinase/streptodornase" rather than "streptokinase/streptodornase for skin testing."

We could not determine the number of patients who received the incorrect dose or the frequency of severe local reactions in our clinical setting. We were unable to find studies in the literature reporting the frequency of severe cutaneous reactions after streptokinase/streptodornase injection for skin testing. In fact, skin testing with this preparation has not yet been approved by the Food and Drug Administration. Nevertheless, it is appropriate to make additional efforts to educate nurses, pharmacists and physicians in the proper ordering, labeling and use of these preparations to prevent the possible complications described associated with highly

concentrated intradermally administered streptokinase/streptodornase.

HOWARD K. STEINMAN
PETER G. TUTEUR, M.D.
Washington University
St. Louis, MO 63110 School of Medicine

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2. Package insert for "Streptokinase-Streptodornase Varidase for Intramuscular Use." Pearl River, New York, Lederle Laboratories

BRONCHOPULMONARY DYSPLASIA IN THE NEWBORN

To the Editor: The recent article by Ehrenkranz et al. and the accompanying editorial by Dr. Northway, discussing the possible role of vitamin E in preventing bronchopulmonary dysplasia, were fascinating. Dr Northway's plea for standardizing diagnostic criteria in therapeutic trials has particular salience. I should like to note that tracheobronchial cellular cytology may be useful for following the course of bronchopulmonary dysplasia and for staging its severity.

Rashe and Kuhns,[1] as well as D'Ablang et al.,[2] have described certain cytologic changes associated with prolonged neonatal ventilation and the development of bronchopulmonary dysplasia.

Tracheal lavage and suctioning are routinely performed as pulmonary toilet for the incubated newborn. The addition of a simple in-line mucous trap facilitates obtaining specimens of the cellular elements. A competent cytologic laboratory can readily distinguish the inflammatory, dysplastic and metaplastic changes described in the above papers.

Dr. Northway's recommendation that rigorously defined diagnostic standards must be used in future studies of bronchopulmonary dysplasia should be heeded. I suggest that the histopathology of recovered cells might be a useful adjunctive criterion.

JOHN W. SCANLON, M.D.
Columbia Hospital for Women
Georgetown University
Washington, DC 20031 School of Medicine

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Letters to the Editor should be typed double-spaced (including references) with conventional margins. The length of the text is limited to 1½ manuscript pages.

ORAL CONTRACEPTIVES AND BIRTH DEFECTS

To the Editor: Rothman and Louik, in the September 7, 1978, issue of the *Journal,* say that "a reasonable interpretation if these data would be that oral contraceptives present no major teratogenic hazard," but this claim is contradicted by actual data.

Despite the large apparent sample size (7723), the effective sample size is too small here to draw valid conclusions about the safety of oral contraceptives. The critical statistical question here is: What is the "power" of the tests used here? What is the chance that if there is a real hazard, the test will detect it? The power here is inadequate. The authors should have been warned of this discrepancy when, even though "The overall prevalence of malformation was about one third greater in the short-interval group than for the nonexposed," the difference was not statistically significant (P=0.05). To argue that failure to reach the 5 per cent level (the authors give P=0.07) shows the absence of a serious hazard is to make a basic mistake.

The following nontechnical argument will suggest why the effective sample size is too small and the power is too poor to warrant the claim that there is no serious hazard. The occurence of malformations that are sensitive indicators of teratogenicity (Down's syndrome is a well known example) are rare events. In this typical Poisson situation, the power depends on the number of rare events that occur rather than on total sample size. Thus, there are only seven reports of Down's syndrome, three in the 1448 births in the short-interval series and four in the remaining 6275 births. Because the effective sample size is so small, even though the observed incidence is about three times higher in the short-interval series, the statistical tests are not "significant." They are, however, doing their job by warning that valid conclusions cannot be drawn from so few data.

If it would be irresponsible to call for a ban on oral contraceptives on the basis of the excess risk of Down's syndrome found here, it is equally irresponsible to issue a reassuring statement on the basis of these data.

IRWIN D. J. BROSS, PH.D.
Roswell Park Memorial Institute
Buffalo, NY 14263 666 Elm St.

The above letter was referred to the authors of the article in question, who offer the following reply:

To the Editor: Dr. Bross warns that the absence of a statistically significant difference should not be equated with the absence of an effect. On this point we strongly agree with him: one of us made the same point in an editorial in the December 14, 1978, issue of the *Journal,* in which it was suggested that use of confidence intervals instead of significance tests avoids the misinterpretation of observed differences that are "not significant." But Dr. Bross also implies that our interpretation of our findings — that oral contraceptives present no major teratogenic hazard — is based merely on a failure to find statistically significant differences. In fact, because we believe statistical significance is a relatively poor criterion by which to judge the strength of an association, we neither mentioned nor considered the statistical significance or non-significance of our findings.

Instead, we based our interpretation on a number of other considerations. In the first place, although the prevalence of malformations was one third greater among infants conceived shortly after cessation of oral contraceptives, the upper limit of the 90 per cent confidence interval corresponded to a 70 per cent increase in prevalence. This finding indicates that a twofold or greater increase in prevalence of malformation after oral-contraceptive use would be highly unlikely. Secondly, for serious defects, we saw no difference whatever in prevalence between nonexposed and those with oral-contraceptive exposure before conception. Thirdly, in three previous follow-up studies, oral contraceptives were unrelated to frequency of malformation among offspring.

For some malformations, including Down's syndrome, a greater prevalence was indeed observed after pill use; other malformations occurred less frequently after pill use. We chose, however, not to focus on any category of malformation for which only a few cases were observed. We did comment on an association with undescended testis, based on several dozen cases and a prevalence ratio of 1.9, with confidence limits ranging from 0.9 to 3.9. Our overall interpretation was guarded, as is made clear by our concluding sentence: "It seems prudent for the present, however, to continue to regard any exogenous hormones taken after conception to be potentially teratogenic, despite the fact that even the studies that implicate non-contraceptive exogenous hormones as teratogenic present little evidence that oral contraceptives have the same effect."

KENNETH J. ROTHMAN, DR.P.H.
CAROL LOUIK, M.SC.
Boston, MA 02115 Harvard School of Public Health