insertion of a copper 7 as 72% (52 patients) had no problems after a second insertion.

A higher incidence of ectopic pregnancy has been recorded in certain instances related to I.U.D. use. We did not find this to be the case in our series, all pregnancies being intrauterine.

Bleeding in association with an I.U.D. is a major cause of removal. It may in part be related to the size of the device; the copper T being larger than the copper 7 has a higher medical removal rate for pain and bleeding.

Like Tatum (1973) we also found an acute reaction to the presence of copper in the peritoneal cavity. Thus a copper 7 should be removed as soon as is practicable after inadvertent perforation of the uterus. If done at an early stage the laparoscope can be used, but later on a laparotomy will be necessary.

In considering any particular I.U.D. discontinuing use of the device for any particular reason is best expressed as a net closure rate as it expresses the probability of this reason occurring in relation to all the other reasons for which closure might be necessary. In considering, however, the probability of a closure for any particular reason happening with one device compared with other devices gross termination rates are preferable. They express the probability of the particular event happening in relation to the total number of people and are always individually higher than the corresponding net rate and cumulative termination rates cannot be used (Tietze, 1967). In order to compare our experience with the copper 7 with the reported data for copper T (Lewit, 1973), Lippes D, and Lippes C (Tietze and Lewit, 1970) gross cumulative termination rates were reported in table IV for the combined, never-pregnant, and parous patients. The combined rates were then compared (table V) with the rates for the other devices. Apart from a higher discontinuation rate for planned pregnancy, which probably reflected the lower parity of patients using the copper devices, the incidence of side effects of the copper 7 in our series was substantially less than in the reported series for the copper T, Lippes D, and Lippes C devices.

The present recommendation of the manufacturers is to change the device after two years of use. Observation of the monthly pregnancy rate shows no further increase after 12 months of use. This suggests that a longer duration of action is probable without adversely influencing the contraceptive efficacy of the device. There were no cases of massive erosion of the copper wire or fragmentation of the coil in the devices removed during the period of study. This is in agreement with the results of Tatum (1973) with the copper T, and we are

currently investigating the use of the copper 7 up to three years of use.

All 1,156 patients had a preinsertion cervical cytological examination, which was repeated annually. No cases of cervical dyskaryosis or atypical cervical cells were reported. In agreement with Tatum's findings there seems to be no added risk of cervical neoplastic change. The two intrauterine pregnancies continued to term with the device in situ. Both pregnancies resulted in normal children without congenital abnormalities. In one the device was spontaneously expelled at 36 weeks, and the other was delivered in the first stage of labour.

Conclusions

From 1,156 insertions of the copper 7 contraceptive device with 15,044 women-months of use we conclude that it offers advantages in intrauterine contraception. Continuity is improved for all users. It is a useful method for those who have not been pregnant and as an exchange device for patients having problems with other intrauterine devices or contraceptive methods. These advantages must be set against the necessity of replacing the copper 7 after a limited life span. In no cases in our series did cervical cytological examination show anything abnormal, and a 98.1% follow up was achieved.

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References

- Lewit, S. (1973). *Studies in Family Planning*, 4, 171.
- Newton, J. R., Elias, J., and Newton, P. (1971). *British Medical Journal*, 2, 642.
- Newton, J. R., Elias, J., and McEwan, J. (1972). *Lancet*, 2, 951.
- Newton, J. R., et al. (1973). *British Medical Journal*, 3, 280.
- Potter, R. G. (1966). *Demography*, 3, 297.
- Potter, R. G. (1967). In *Proceedings, Sydney Conference*, p. 869. New York, International Union for Scientific Study of Population.
- Sivin, I. (1973). *Studies in Family Planning*, 4, 162.
- Tatum, H. J. (1973). *American Journal of Obstetrics and Gynecology*, 117, 602.
- Tietze, C. (1962 a). *First Progress Report on Intrauterine Contraceptive Devices*. New York, National Committee on Maternal Health.
- Tietze, C. (1962 b). *Excerpta Medica International Congress Series*, 54, 9.
- Tietze, C. (1967). *Studies in Family Planning*, 18, 1.
- Tietze, C., and Lewit, S. (1970). *Studies in Family Planning*, 1, 1.
- Westrom, L., and Bengtsson, L. P. (1970). *Journal of Reproductive Medicine*, 5, 154.
- Zipper, J., et al. (1969). *American Journal of Obstetrics and Gynecology*, 105, 1274.

MEDICAL MEMORANDA

Nephrotic Syndrome with Oat-cell Carcinoma

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The association between the nephrotic syndrome and extrarenal malignancy (Galloway, 1922; Lee *et al.*, 1966; Miller, 1967; Ghosh and Muehrcke, 1970; Lewis *et al.*, 1971; Loughridge

and Lewis, 1971; Couser *et al.*, 1973; Gault *et al.*, 1973) suggests an immunological pathogenesis (Lewis *et al.*, 1971; Loughridge and Lewis, 1971; Couser *et al.*, 1973; Gault *et al.*, 1973), possibly related to the glomerular deposition of antibody to tumour antigen (Avrameas and Ternynck, 1969; Lewis *et al.*, 1971; Loughridge and Lewis, 1971; Couser *et al.*, 1973; Gault *et al.*, 1973). We report a case of oat-cell carcinoma of the lung presenting as the nephrotic syndrome. The latter was associated with the presence of antinuclear antibody (A.N.A.) in the serum and glomerular deposition of IgG and complement. The presence of large amounts of extracellular DNA in necrotic tumour tissue and Feulgen-positive deposits within the glomerular basement membrane suggested the possibility that tumour-induced anti-DNA might have resulted in this immune-complex glomerulonephritis with nephrosis.

Case Report

A 42-year-old white man presented with a four-week history of dyspnoea, cough, back pain, increasing abdominal girth, and pedal oedema. He was pale and had bilateral pulmonary basilar rales, an

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FIG. 1—Section of lung tumour showing area of necrosis with extracellular nuclear material (arrowed). (Feulgen stain. $\times 672$.) FIG. 2—Glomerulus showing capillary wall thickening and subepithelial intramembranous deposits (arrowed). (Masson's trichrome. $\times 672$.) Similar masses were seen with Feulgen stain superimposed on silver methenamine stain. FIG. 3—Electron micrograph of glomerular capillary wall showing subepithelial electron-dense deposits. ($\times 4,244$.) FIG. 4—Glomerular granular deposition of IgG in mesangium and along capillary loops visualized with fluoresceinated goat antihuman IgG. ($\times 382$.)

enlarged liver, ascites, and peripheral oedema. The urine contained numerous red blood cells, 1-3 coarsely granular casts per high-power field, and 10 g protein in a 24-hour collection. Normal serum values were obtained for urea nitrogen, creatinine, and electrolytes but serum cholesterol was 340 mg/100 ml and albumin 1.8 g/100 ml. Serum globulin was slightly increased (4.2 g/100 ml), due mainly to alpha-fractions 1 and 2. The serum concentration of the third component of complement (C'3) was 360 mg/100 ml (normal for this laboratory 145 ± 22 mg). The serum showed a diffuse nuclear pattern for A.N.A. at a 1/20 dilution. Chest x-ray examination showed mediastinal widening and a left hilar mass. Oat-cell carcinoma was detected in a left scalene node biopsy specimen and in a smear of sternal bone marrow. Before chemotherapy could be started the patient developed severe thrombocytopenia and recurrent epistaxis and died suddenly.

Pathological Findings.—Necropsy showed oat-cell carcinoma of the left main-stem bronchus with metastases in multiple lymph nodes, liver, adrenal glands, and multiple vertebral bodies. There was no evidence of tumour producing venous obstruction, renal infiltration, or amyloid disease. Areas of necrosis in the primary tumour and metastases stained positively for DNA in an extracellular location using Feulgen stain (fig. 1). Glomerular basement membrane thickening was shown by light microscopy. Subepithelial intramembranous deposits were seen as red masses with Masson's trichrome stain, as dense deposits by electron microscopy, and as IgG and C'3 by immunofluorescent techniques (figs. 2-4). These deposits appeared as large discrete spikes or rounded masses, pink with Feulgen stain, projecting towards the epithelial cells from the basement membranes, outlined by previous staining with silver methenamine. The specificity of this staining technique for DNA was confirmed by the use of the same technique on sections of kidney from a patient known to have lupus nephritis. A negative control was derived using biopsy sections from a patient with membranous glomerulonephritis. All the specimens were coded and read "blind" by an independent pathologist. Feulgen-positive deposits were seen only in the patient with lupus nephritis and in the subject of this report. An attempt was made to elute the immunoglobulins from tumour and kidney using a polymer technique modified from Avrameas and Ternynck (1969), but insufficient protein was obtained to allow any identification of cross-reactivity between the two eluates in agar gel. The kidney eluate showed weak antinuclear activity demonstrated by the indirect immunofluorescent technique with rat kidney as substrate.

Comment

Though the nephrotic syndrome has been reported in association with extrarenal malignancy (Galloway, 1922; Lee *et al.*, 1966; Miller, 1967; Ghosh and Muehrcke, 1970; Lewis *et al.*, 1971; Loughridge and Lewis, 1971; Couser *et al.*, 1973; Gault *et al.*, 1973) the mechanism of the glomerular damage has not been clarified. The findings in this and other cases suggest that immune-complex deposition is central to the pathogenesis of this lesion. Some workers have suggested that deposition of immunoglobulins is related to the production of a specific antigen by the tumour (Lewis *et al.*, 1971; Gault *et al.*, 1973). In this case there was no history or clinical or pathological evidence to suggest pre-existing disseminated lupus erythematosus or any other form of renal disease. The presence of large quantities of extracellular DNA in necrotic tumour tissue, serum antinuclear antibody activity, and Feulgen-positive deposits within glomerular basement membranes suggests an alternative mode of pathogenesis—namely, antibody formation against nuclear antigen released by tumour necrosis. Similar cases should be studied in an attempt to confirm such a possibility.

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References

- Avrameas, S., and Ternynck, T. (1969). *Immunochemistry*, 6, 53.
- Couser, M. G., *et al.* (1973). *American Society of Nephrology, Abstract*, p. 26.
- Galloway, J. (1922). *British Medical Journal*, 2, 1201.
- Gault, M. H., Kaplan, B. S., and Cherito, E. (1973). *American Society of Nephrology, Abstract*, p. 39.
- Ghosh, L., and Muehrcke, R. C. (1970). *Annals of Internal Medicine*, 72, 379.
- Lee, J. C., Yamauchi, H., and Hopper, J. (1966). *Annals of Internal Medicine*, 64, 41.
- Lewis, M. G., Loughridge, L., and Phillips, T. M., (1971). *Lancet*, 2, 134.
- Loughridge, L. W., and Lewis, M. G. (1971). *Lancet*, 1, 256.
- Miller, E. G. (1967). *Annals of Internal Medicine*, 66, 507.