VP-16, VM-26 varies with a factor of two, cisplatin, carboplatin, BCNU, and TCNU with a factor of eight. In the comparison of patterns in sensitivity, the cell lines most sensitive to epipodophyllotoxines and anthracyclines proved least sensitive to platin and nitrosourea and vice versa. By continuous exposure to daunorubicin a five-fold resistant cell line was obtained. Compared to the parental cell line, the same collateral sensitivity was obtained on this cell line, as is was cross-resistant to adriamycin and VP-16 and expressed an increased sensitivity to cisplatin and BCNU. From these results it is tempting to explain the clinical synergy of platin and epipodophyllotoxines as a cytotoxic action on different subclones within the tumor.

HETEROGENEIC EXPRESSION OF BLOOD GROUP A AND H ISOANTIGENS IN BLADDER TUMOURS: ASSOCIATION WITH MEAN NUCLEAR VOLUME.
K.Nielsen and T.Ørntoft. Institute of Pathology, Aalborg Hospital, DK-9000 Aalborg and Danish Cancer Society, DK-800 Aarhus C, Denmark.

To elucidate the well known heterogeneity in the ability to express blood group ABO isoantigens in transitional cell carcinomas, a stereological estimate of the mean nuclear volume in areas expressing blood group antigen was compared to the estimate from areas of identical pathological grade where the antigen expression was deleted. Mean nuclear volume were estimated from antigen positive and antigen negative areas in sections from 21 blood group 0 and 20 blood group A individuals using an indirect peroxidase method with monoclonal anti-H and anti-A antibodies. The mean nuclear volume increased as expected with increasing pathologic grade. In blood group 0 individuals the mean nuclear volume was 241 μm^3 in positive areas and 338 μm^3 in negative areas ($2p<0.0005$) of identical pathologic grade. In A individuals the mean nuclear volume was 217 μm^3 in positive areas, and 351 μm^3 in negative areas ($2p<0.0025$). The results indicate a complex biological nuclear mecanism associated with the cellular ability to express blood group antigens.

HETEROGENEITY OF HIGH-ENERGY PHOSPHATE COMPOUNDS IN TWO SCLC XENOGRAFTS BEFORE AND AFTER X-IRRADIATION.
P.E.G. Kristjansen, E.J. Pedersen, B. Quistorff and M. Spang-Thomsen. Dept. of Oncology, Finsen Institute; Institutes of Chemistry, Biochemistry, and Pathological Anatomy, University of Copenhagen.

The in vivo levels of ATP and inorganic phosphate (Pi) were measured in two sublines derived from a single human small cell lung cancer (SCLC). The tumors were serially grown in nude mice. The tumor line CPH SCC 54A is more radiosensitive than 54B in spite of similar growth characteristics. The metabolites were measured by in vivo 31-P-MR-spectroscopy and biochemical analysis of extracts of freeze-clamped tumors. During untreated growth a slow decline in ATP:Pi ratio was seen in both tumors. In 54A the ATP:Pi was significantly higher than in 54B. Irradiation of the tumors with 20 Gy induced an immediate decrease in ATP:Pi with a nadir at 6-12 hours followed by a gradual increase to pretreat- ment levels within 72 hours. The decrease was faster in 54A with a $T_{\frac{1}{2}}$ of 2.5 hours against 6 hours in 54B. This study demonstrated a difference in energy metabolism as well as in the metabolic response to irradiation in two SCLC sublines from the same original tumor.

CLONAL HETEROGENEITY DEMONSTRATED BY FLOW CYTOMETRY AND CHROMOSOME ANALYSIS AS A FACTOR IN THE DEVELOPMENT AND PROGRESSION OF COLORECTAL CANCER.
Steffen Ellebæk Petersen and Henrik Sloth. The Danish Cancer Society, department of clinical experimental oncology, Nørrebrogade 44, DK 8000 Århus C, Denmark.

The theory of clonal evolution of tumours is mainly based upon cytogenetic analysis of the progression of hematologic malignancies, whereas similar studies on solid tumours are few. Ploidy analysis of 51 colorectal adenomas by flow cytometry (FCM) showed the occurrence of smaller or larger DNA-aneuploid cell populations in 17, with a clear correlation to adenomas with severe dysplasia. Chromosome counting on metaphase spreads from 8 adenomas with moderate dysplasia and 2 with severe dysplasia revealed modal values in the range of 45-50, but 18% of the metaphase counts were scattered in the range 51-110. None of these adenomas showed corresponding aneuploid peaks in the DNA histograms. This indicates that benign adenomas continuously develop a number of aberrant methaphases, which do not form quantitatively significant subpopulations, discernible by FCM. However, selection of one of these may start an aneuploid, possibly more dysplastic clone. FCM of multiple biopsies from 120 colorectal carcinomas showed that 71 (59%) had only one cell population (either diploid or aneuploid). Forty-nine (41%) had 2 or more cell populations with different DNA ploidy either mixed in the tumour or dominating distinct areas. This frequently seen heterogeneity was significantly correlated to a bad survival, but also to advanced tumour stage. Diploidy versus aneuploidy did not give any prognostic information. In a multivariate regression analysis tumour stage was the dominant prognostic factor, with insignificant additional information from DNA heterogeneity.