within the hepatic duct for the relief of obstruction by extrinsic carcinoma (cf. Cattell, 1943; Grey Turner, 1955; McGoon and Clagett, 1958).

The fact that the obstruction was in this instance extrinsic was perhaps a favourable circumstance with regard to permanent intubation, in contrast with carcinoma involving the wall or lumen of the bile-duct.

A special tube has been designed for trial in future cases of inoperable malignant obstruction of the common bile-duct (Fig. 2 A). Two possible ways of employing this tube are suggested: (1) to site the bulb above the obstruction after removing excess tubing above the bulb (Fig. 2 B); the latter would then prevent downward sliding of the tube; and (2) if it is impossible to pass the bulb upwards through the obstruction the bulb end may be trimmed and sited inferiorly at the ampulla with a suitable length of tubing passing up proximally through the narrowed duct (Fig. 2 C).

We wish to thank Dr. Steele, of Portland Plastics, Hythe, Kent, for producing this tube.

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Preliminary Communications

Clinical Significance of Ploidy in Carcinoma of Cervix: Its Relation to Prognosis

Very little is yet known about the significance of the chromosomal changes in human tumours. This lack of knowledge stems largely from the technical difficulties associated with chromosomal analysis in tumours; such data as are available seem to indicate an almost infinite variety of changes, and one is tempted to question whether these changes bear any significant relation to the clinical features of the tumours. In general, two types of chromosomal change may be recognized: (1) numerical or structural changes involving a greater or lesser number of individual chromosomes and (2) a change to a tetraploid state—that is, doubling of the chromosome complement by endomitosis or some other mechanism. Whereas the former has occurred in most (if not all) tumours, only a fraction, perhaps about a half, have become tetraploid.

It is well established that the amount of deoxyribonucleic acid (D.N.A.) in a cell bears a relation to its chromosome number. The technique of microspectrophotometry may be used to measure the D.N.A. content of interphase cells in tumours irrespective of the presence of cells in mitosis suitable for chromosome counting. Using the modal D.N.A. content of interphase cells as a measure of their chromosome complement, it was previously shown that cervical carcinomata fell into two broad but clearly defined groups, centred at the hyperdiploid and tetraploid levels respectively (Atkin, Richards, and Ross, 1959). We have recently reviewed these cases, together with 18 further cases (adenocarcinomata have been excluded from the present study), and it is now clear that the patients in the tetraploid group have on the whole done better (all patients were treated initially by radiotherapy, a few subsequently undergoing surgery). This was unexpected, as previous results had suggested that *local* recurrences (which occurred in only about 10% of cases) were commoner in tumours with high chromosome numbers.

In a study of the histological sections of these cases, to be reported in detail later, we have found that their ploidy could usually be deduced from the predominant nuclear size, although it was noted that a minority appeared to show variation in ploidy in different parts of the section. It seemed worth while examining the sections of a series of cases treated by radiotherapy in the past. Unfortunately many cases had to be rejected because of poor preservation of the nuclei; however, an assessment of the predominant nuclear size—that is, whether diploid or tetraploid—was made in 94 cases.

TABLE I.—*Relationship Between Ploidy, as Indicated by D.N.A. Content and Nuclear Size, and Subsequent Course of the Disease in 224 Cases of Carcinoma of the Cervix. For the Cases Where Nuclear Size was Estimated, the Five-year Results are Shown; for the Others, the Follow-up Period Varies but is on the Average 48 Months (See Text)*

	Clinical Stage								Total	
	I		II		III		IV			
	Well	Rec.	Well	Rec.	Well	Rec.	Well	Rec.	Well	Rec.
Diploid class:										
Based on D.N.A. content	11	9	5	15	3	14	—	9	19	47
Based on nuclear size	6	5	7	14	1	5	—	5	14	29
Total	17	14	12	29	4	19	—	14	33	76
Tetraploid class:										
Based on D.N.A. content	14	9	11	12	7	6	—	5	32	32
Based on nuclear size	7	2	13	5	1	12	—	11	21	30
	21	11	24	17	8	18	—	16	53	62
P	0·14		0·0059		0·15		—		0·0056	

Rec. = Alive with, or has died from, recurrence.

The results are shown in Table I. Where the ploidy was estimated from the D.N.A. content, the figures are based on the patients' most recent follow-up appointment (the mean follow-up period of patients who have survived was 48 months; the minimum was 21 months); where the estimation was made from the nuclear size, the five-year cure-rate is shown. The overall figures show a highly significant difference in cure-rate in favour of the tetraploid group. Stage I cases show a slight difference that is not statistically significant. Stage II cases, however, show a highly significant difference. For stage III the figures for all the cases are not significant, but they are significant ($P=0.039$) if only those cases in which ploidy was estimated from D.N.A. content are considered (the better figures for these cases, as compared with those in which nuclear size was estimated, may be due to their slightly shorter average follow-up period and to the use in recent years of supervoltage radiotherapeutic techniques).

Since it was uncertain whether the difference in prognosis resulted from a difference in radiosensitivity or whether it perhaps reflected a difference in the rate of spread of the disease, it was decided to obtain further data from a series of cases treated by surgery alone.

The histological sections from 108 cases of squamous-cell carcinoma of the cervix treated by surgery were therefore studied. (We are indebted to Dr. A. C. Thackray and Dr. A. D. Thomson, of the Bland-Sutton Institute of Pathology, for the opportunity to study these sections.) Ten cases were excluded because of poor preservation of the nuclei; the ploidy of the remainder was assessed, as before, on the basis of nuclear size. The 10-year cure-rate indicates a significantly better prognosis for the tetraploid class (P=0.016) (Table II).

TABLE II

	Alive (No Evidence of Recurrence)	Died
Diploid class	13	31
Tetraploid ,, ...	25	23

Six patients are excluded from Table II who, though alive and well when last seen, had been followed up for less than 10 years: one diploid and three tetraploid for from 5 to 10 years, and two tetraploid for from 2½ to 5 years. The incidence of glandular metastasis on microscopical examination was significantly higher in the diploid class, and it was noteworthy that of 10 patients with glandular metastasis in the tetraploid class five were nevertheless alive and well after 10 years (as compared with only 1 out of 14 in the diploid class).

It appears, therefore, that the relationship between ploidy and prognosis can be explained in terms of the biological attributes, other than radiosensitivity, of the tumour; tumours in the diploid class are more likely to have spread beyond the limits indicated by the clinical assessment of the disease.

In the course of the present study a correlation has also been found between ploidy and degree of differentiation. When the sections were classified into three grades, following Martzloff (1923), it was found that, whereas most of the tumours in the undifferentiated (spindle-cell) grade were diploid, tetraploid tumours predominated in the other two grades. It is of interest that the relation between ploidy and prognosis appears to be independent of that between ploidy and histological grade. Thus of 182 tumours in the intermediate (transitional-cell) grade, only 17 out of 61 in the diploid group, as compared with 57 out of 121 in the tetraploid group, remained well (P=0.012).

Wentz and Reagan (1959), classifying cervical carcinomata into a "small-cell malignant tumour, a large-cell non-keratinizing cancer, and a keratinizing cancer," found a better prognosis for the large-cell and the keratinizing groups than for the small-cell group (the majority of their cases received radiotherapy). Although their classification differs in detail from the present one, their follow-up results probably reflect the same biological principles that underlie the present results.

As mentioned earlier, variation in nuclear size was sometimes seen in the histological sections, and it appears that some tumours, particularly those with a high incidence of endomitosis, have both diploid and tetraploid cells in a more or less intimate mixture. On the other hand, most tumours showed consistency of ploidy even when sections taken from different regions were examined. Perhaps a fair comment on the present findings would be that the influence of ploidy on prognosis may well be more pronounced than appears from the above results, but that the overall picture is modified by variation of ploidy in some tumours.

We are indebted to Dr. L. H. Gray, F.R.S., for helpful discussion. This work was supported by a grant from the British Empire Cancer Campaign.

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Meclozine ("Ancoloxin") and Foetal Abnormalities

Preliminary Report by the Epidemic Observation Unit of the College of General Practitioners

In July, 1962, the College set up a Register of Unexpected Toxicity to collect reports from its own members and from others (*Brit. med. J.*, August 11, p. 408) about any association between unexpected toxicity or side-effects in patients (or their offspring) and the previous consumption of drugs, whether new or well known.

Among others so far received, 29 reports have related to mothers who took anti-emetic drugs for nausea or vomiting in pregnancy and who subsequently gave birth to a live deformed baby or suffered the intrauterine death of a foetus. Of these 29 reports, 10 relate to "ancoloxin" (B.D.H.: meclozine hydrochloride and pyridoxine hydrochloride). About pyridoxine, apart from its combination with meclozine, we have registered three other reports. An urgent search was begun on October 16 by a team of nineteen doctors in the College under Dr. P. A. Walford through their records of 784 pregnancies, fully documented as regards drugs, illness, immunizations, and outcome. Most of the patients were attended since September 30, 1961; among these there were 124 mothers who had been given drugs for treatment of nausea or vomiting during the first twelve weeks of pregnancy. Of these, three had malformed babies, and each of these mothers had taken ancoloxin.

The congenital abnormalities registered in our ten reports about ancoloxin are as follows: (1) meningocele; (2) meningocele, hydrocephalus, and bilateral talipes; (3) meningomyelocele, flaccid legs, and patulous anus; (4) spina bifida, microcephaly, and hydrocele; (5) hypoplasia of lungs, kidney, and gall-bladder; (6) imperforate anus; (7) rudimentary thumb; (8) vascular naevus on neck; (9) bilateral talipes; (10) pyloric stenosis.

In view of this mounting evidence against the safety of ancoloxin in pregnancy, information as it was received by the College was passed to the medical adviser of British Drug Houses Limited from time to time, the first six reports being sent on October 22, 1962. It is now felt that the College has a duty to publish the information which has reached it about ancoloxin, in the hope that further investigations can be carried out by others to determine what effect, if any, meclozine and pyridoxine, separately and together, may have upon foetal development. In the meantime the College wishes to draw the attention of all doctors to the information here presented.

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