positive gain varying between 1 and 4% during the 210 minutes of observation.

Response of Individuals to the Three Different Inhalations

The serial indirect M.B.C. readings of each individual after the three test inhalants have been scrutinized.

After the inhalation of deptropine citrate alone, the highest reading of 14 of the 20 patients occurred between 150 and 210 minutes; the highest reading of the remaining patients occurred at 90 minutes (two patients), at 120 minutes (two patients), and at 60 minutes in one patient. The trial had to be discontinued after 15 minutes in one patient owing to severe asthma. Four individuals were substantially worse 15 minutes after the inhalation of deptropine citrate—that is, all these patients showed a drop in their indirect M.B.C. of 25% or more. None of these four patients, who showed this marked deterioration after the inhalation of deptropine citrate, showed a similar deterioration after the inhalation of the inert propellant.

After the inhalation of deptropine citrate and isoprenaline, the highest reading was observed at 15 minutes (six patients), at 30 minutes (two patients), at 60 minutes (three patients), at 90 minutes (one patient), at 120 minutes (three patients), at 180 minutes (two patients), and at 210 minutes (three patients). Roughly half the patients showed a sustained effect after reaching their peak indirect M.B.C. over the 210-minutes period of observation.

Fifteen minutes after the inhalation of the inert propellant there was only one patient who showed an improvement of 10% or more in the indirect M.B.C., most patients showed a slight drop. Peak readings of individuals after the inhalation was uniformly scattered throughout the 210 minutes of observation, but, as the group results showed, there was a general tendency for values to increase by 3 to 4% throughout the morning.

Discussion

The 20 asthmatic individuals reported in this investigation were included in an earlier comparative study on the effect of some adrenergic drugs and atropine methonitrate given by inhalation (Kennedy and Thursby-Pelham, 1964).

On comparing the result of this earlier study with the present investigation it is clear that the time-response curve after deptropine citrate is very similar to that obtained after atropine methonitrate. The earlier investigation showed that isoprenaline alone gave a time-response curve of short duration. However, isoprenaline combined with deptropine citrate gave an immediate and sustained effect which was very similar to the time-response curve observed in the present investigation after the inhalation of isoprenaline combined with deptropine citrate.

Deptropine citrate given alone produces nothing startling in the way of the usual atropine-like side-effects, but the asthma condition of four subjects investigated was worse immediately after the inhalation. In previous studies on the same 20 patients with atropine methonitrate alone, one individual showed a similar adverse response; after the inhalation of isoprenaline combined with deptropine citrate this same individual developed severe asthma at 30 minutes.

Summary

A comparative study of the effect on 20 asthmatic individuals of aerosols containing inert propellant, deptropine citrate alone, and deptropine citrate combined with isoprenaline is reported.

The inert propellant was inactive. Deptropine citrate aerosol alone is only effective in producing bronchodilatation after a latent period of one hour, whereas the combined deptropine citrate and isoprenaline aerosol is immediately effective and gives a sustained effect.

I am indebted to the staff of the Department of Respiratory Physiology for carrying out the investigations described in this report, especially Mr. James Booth, S.R.N., Mr. Peter Wilkes, S.R.N., Mr. Norman Curnock, S.R.N., Mrs. Sheila Clarke, S.R.N., and also to Mrs. K. Tattersfield, who prepared the Chart.

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Conserving Ovarian Tissue in Treatment of Ovarian Neoplasms

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When an apparently benign ovarian cyst on histological examination reveals an unsuspected carcinoma a decision on what to do next can be one of the most difficult of clinical problems. The possibilities of further management include: (a) another operation for removal of the other ovary, (b) another operation for removal of the uterus and the other ovary, (c) external irradiation with or without intrauterine radium insertion, and (d) no radiotherapy, no further operation.

Material

In an attempt to provide some information of value in deciding which course to take, we have followed up the ovarian neoplasms treated by unilateral ovarian cystectomy

or oophorectomy at Chelsea Hospital for Women during 1948-55. There were 100 such patients, permitting a follow-up ranging from 7 to 14 years. Of these, 63 were traced; mucinous cyst was found to be most common (24), and next the dermoid cyst (16). Benign neoplasms numbered 50, the remaining 13 being classified as malignant.

However, the distinction between a benign and a malignant cyst is not always clear-cut, but a distinction is important both clinically and histologically, since future management is governed by it. There are specimens of cyst in which only a small area of carcinoma is observed on examination, but a

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small lesion may be overlooked unless a diligent naked-eye search is always made.

A more difficult kind of specimen is one in which the cellular activity is such that, though the full picture of carcinoma is absent, malignancy is suggested by the appearance of the epithelial pattern; there is slight-to-moderate enlargement in the size of the cell and the nucleus, maybe with hyperchromatism. These changes can be present in one or several areas but without invasion of the supporting stroma. Such cases may be classified as borderline, and in practice they constitute only a small fraction of any group; but this borderline category is important because it should ensure that patients with a tumour of doubtful nature are followed up. These histological findings are uncertain as guides to prognosis, but they emphasize the possibility of recurrence.

All the sections from patients in the group initially recorded as malignant were re-examined "blind" at the time of the present survey, the pathologist not knowing the original report; this was confirmed in all cases except two, and these are included in the benign group in Table I.

TABLE I.—Classification of Cases

Benign		Malignant	
Mucinous cystadenoma	24	Mucinous cystadenocarcinoma	8
Dermoid cyst	16	Adenocarcinoma	3
Fibroma	2	Papilliferous cystadenocarcinoma	2
Serous papillary cyst	7		
Uncertain	1		
	50		13

Case 1.—A married woman had had a left ovarian cyst removed at the age of 25. The specimen was multilocular, measured 22 by 16 by 10 cm., and contained mucinous fluid. One locule was filled with solid tumour 7 cm. in diameter. A section from this part of the tumour revealed a well-differentiated mucinous carcinoma, but on review this was regarded as only a cystadenoma.

Case 2.—A married woman had had a thick-walled left ovarian cyst removed at the age of 46. The cyst, 20 cm. in diameter, was unilocular with mucinous contents, but there was a small area of "daughter cysts" at one point of the wall that was thought to be a well-differentiated mucinous carcinoma with some areas of benign epithelium. On review this was regarded as a borderline case.

It seems that there may be a tendency to make a diagnosis of ovarian carcinoma too readily and that in the light of experience certain tumours regarded as carcinoma might better be placed in a borderline group.

A third case was considered in the borderline category from the outset and appears in the benign group in Table I.

Case 3.—In this patient, at the age of 34, the left ovary was represented by a thin-walled cyst 12 cm. in diameter filled with clear yellowish fluid. The outer surface was smooth and the inner surface bore numerous small papillomatous outgrowths. A wedge of the right ovary had been removed because of a surface nodule. In both ovaries papillary cystadenoma was observed but no further treatment was undertaken. The patient was kept under observation at increasing intervals after two years. Eight years after the first operation she underwent a laparotomy, followed by radiotherapy, and ultimately, in 1963, excision was carried out. An indeterminate mass of serous carcinomatous type was found, though the epithelial element seemed rather inactive. She remained well during the subsequent 12 months.

The total number of cases of carcinoma of the ovary seen during 1948–55 was 140, and in 39 (28%) the patient survived.

Results of Treatment

The results in all cases of carcinoma of the ovary occurring during the period under review are shown in Table II. By radical surgery it is meant that an effort was made to remove both ovaries and any other tumour in the pelvis, and this often included total hysterectomy. Radiotherapy was used in addition as a palliative in cases where surgery was incomplete.

Those cases under the heading of advanced disease showed evidence of spread through the ovarian capsule and on to surrounding peritoneum and other organs, while disease confined to the ovary showed neither of these characteristics.

TABLE II.—Results of Treatment

	Total No. of Cases		Total No. of Survivors	
	Treated by Radical Surgery and Radiotherapy	Treated by Unilateral Oophorectomy or Ovarian Cystectomy	Advanced	Confined to One Ovary
	Advanced	Confined to One Ovary		
1948	16	1	5	1
1949	13	1	0	0
1950	10	0	1	0
1951	15	1	3	1
1952	15	2	3	2
1953	18	4	7	2
1954	23	3	5	2
1955	17	1	6	1
	127	13	30	9

Table II shows that of a total of 140 patients with carcinoma only 39 (28%) survived five years or more, but when the disease was confined to one ovary the survival rate was strikingly high, nine surviving out of 13 patients with carcinoma in cysts. This difference may be ascribed to slower growth of a biologically less active tumour or to fortuitous early diagnosis of an ovarian cyst in which carcinoma has not had time to penetrate the capsule. The type of growth and age at operation are known, and it is interesting that the age-groups of malignant and benign tumours in this series correspond closely—malignant 25–59 years and benign 23–59 years of age at operation. The benign group of cases, with one exception, showed no further neoplastic activity, and the two patients in whom borderline changes were found on reassessment have remained free of disease.

Ovarian function following operation was normal in the women of premenopausal age, and three of them became pregnant after removal of a carcinoma. In two of these patients the pregnancy had no apparent effect on the disease, though there were signs of recurrent growth in the third by the time she was pregnant for the second time.

Discussion

The results from this hospital show that when the cyst removed at operation is found on histological examination to be malignant the chances of survival are good even if nothing further is done. This is in contrast with the poor results above for cases of more advanced disease. On the evidence presented it would seem that nothing is to be lost by leaving a functioning ovary even though a carcinoma has been removed from the opposite side. Certainly there is no case for removal of both ovaries in a young woman because of a suspicion of malignancy at laparotomy or after an adverse laboratory report has been received.

Randall *et al.* (1962), writing from New York State, have discussed this problem in the light of their findings that of 345 patients followed for 5 to 31 years (a 76% complete follow-up) 24 developed another neoplasm in the conserved ovary at times varying from 2 to 21 years post-operatively. They found little tendency for these neoplasms to repeat the same type of tumour (except for dermoids), and of the 24 cases only four were malignant.

The data recorded here suggest that no further treatment is necessary in the majority of patients in whom carcinoma is an incidental finding in an ovarian cyst. If radiotherapy or further surgery is to be considered, as they will probably be in every case, the evidence analysed here would seem to show that surgery cannot help, because, judging by the survival rate, it is unlikely that any growth will be found in the opposite

ovary. Radiotherapy in the form of external irradiation together with intrauterine irradiation may be advised as an insurance if continuing ovarian function is not thought necessary; but the same considerations apply as for surgery.

Summary

Of 100 patients with ovarian neoplasms treated by unilateral ovarian cystectomy or oophorectomy 63 were followed up from 7 to 14 years after operation; 50 had benign neoplasms and in 13 the tumour was malignant.

In some cases—two in this series—distinction on pathological grounds between the benign and the malignant is not always clear, and "borderline" cases should come under consideration for a proper follow-up with limited treatment.

Against a background of a further 140 patients with bilateral ovarian carcinoma, of whom 39 (28%) survived, only one patient from whom a benign cyst was removed showed evidence of any further neoplastic activity; one borderline case recurred, and 9 out of 13 with definite carcinomas survived five years or more. Two patients reassessed as borderline cases survived.

It is suggested that no further treatment, surgery, or irradiation is necessary in the majority of patients in whom carcinoma is an incidental finding in an ovarian cyst in a young woman.

We gratefully acknowledge the approval of the Medical Committee, Chelsea Hospital for Women, to use case records of their patients.

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Maternal Complications of Rhesus Iso-immunization

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The maternal complications associated with rhesus iso-immunization are the results of different pathogenic mechanisms. The occurrence of afibrinogenaemia after the prolonged retention of a dead foetus probably follows the release of placental thromboplastin into the maternal circulation. Hydramnios can result when the mouth and fauces of the hydropic foetus are so oedematous as to interfere with the swallowing of liquor amnii. The high incidence of pre-eclamptic toxæmia is probably related to the state of "hyperplacentalosis"; and defective placental implantation, or the mechanical problem of accommodating a bulky hydropic placenta, may be the cause of antepartum haemorrhage (Scott, 1958). No mechanism has been suggested to account for the sudden onset of massive dependent oedema of the mother's legs, with no other signs of toxæmia, which sometimes occurs between the 28th and 36th week of a pregnancy complicated by hydrops foetalis.

There is a further rare but well-accepted maternal reaction to a foetus with an incompatible blood group *in utero*. It was first described nearly 50 years ago and re-emphasized by Scott in 1958. This reaction, the onset of which is acute, is manifested by a general illness, and signs of jaundice, pruritus, haemolytic incidents, and oliguria or anuria. Death may supervene. The clinical picture is very similar to that seen after a transfusion of incompatible blood, and it seems likely that in cases of rhesus iso-immunization the syndrome results from foetal red cells, or the products of their haemolysis, passing into the maternal circulation. The following case illustrates the syndrome.

CASE REPORT

A woman, aged 25, conceived for the first time in 1955. During that pregnancy her blood group was found to be O rhesus-negative. No rhesus antibodies were detected in her serum. The pregnancy was uneventful and at term she delivered a healthy, unaffected male child weighing 8 lb. (3.63 kg.).

In 1957 the patient delivered normally and at home a second baby, a daughter weighing 6 lb. 12 oz. (3.06 kg.). During this pregnancy her blood was not examined for rhesus antibodies.

In 1960 the patient attended the Liverpool Maternity Hospital at the eighth week of her third pregnancy. Examination of her blood at that time revealed the presence of rhesus antibodies when the test was performed on both saline and albumin suspensions. At 37 weeks' gestation a positive antibody test was obtained on serum diluted 1 in 4 volumes. The patient remained well, did not develop oedema, proteinuria, or hypertension, and delivered a female child normally at term. The baby weighed 6 lb. 13 oz. (3.09 kg.), and immediately after birth its cord blood gave a positive Coombs test, and showed a haemoglobin concentration of only 83% (12.3 g./100 ml.) and a serum bilirubin level of 7 mg./100 ml. An immediate exchange transfusion was carried out and the child subsequently made good progress.

Investigation in 1960 of the patient's husband showed his blood group to be O rhesus-positive, the probable genotype being CDe/cDe.

In November 1962 the patient, then aged 32 years and pregnant for the fourth time, was once more booked for confinement at hospital. Examination of her blood at the tenth week of pregnancy again revealed the presence of rhesus antibodies when the serum was tested against cells suspended in either saline or albumin solutions.

Until the 31st week of gestation the pregnancy continued uneventfully and the patient was physically well in every respect.

At the 32nd week, however, it was noted that her feet and legs had become very swollen, with gross pitting oedema. But the blood-pressure and urine remained normal. The haemoglobin level was 73% (10.8 g./100 ml.) and the rhesus antibody test positive at a titre of 1 in 10 volumes. On abdominal examination at that time the uterus was found to be tense and its size was that of a 36 weeks pregnancy. Foetal heart sounds were not audible and no foetal movements were felt. This sudden increase in uterine size was attributed to hydramnios, and subsequently this diagnosis was confirmed by a torrential gush of liquor following rupture of the membranes during labour.

Radiological examination at the 32nd week of pregnancy showed a foetus of corresponding maturity whose attitude *in utero* was typical of hydrops foetalis.

At the 33rd week the patient was admitted to hospital for induction of labour. She was given a soap enema, and, as the foetus was already dead, four doses of quinine sulphate, 5 gr. (325 mg.) orally, at half-hourly intervals. This produced no uterine response, so an intravenous infusion of 10% dextrose, containing two units of oxytocin (Syntocinon) in one litre, was started. The patient was in