# FURTHER STUDIES OF TREATMENT OF ADVANCED AND RECURRENT CARCINOMA OF CERVIX BY MEANS OF CHEMOTHERAPY

by

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Management of advanced cases of carcinoma of the cervix as well as the group of cases where the disease has recurred following surgery and/or radiotherapy poses difficult problems not only to the gynaecologists but also to the radiotherapists. The terminal ending of these conditions will lead an increasing number of women to a malodorous and painful death. Cytotoxic drugs have been used in these circumstances with the object of relieving the subjective symptoms and also of inhibiting the progress of the tumour.

At the third All India Cancer Congress, a report based on the treatment of 36 cases of carcinoma of the cervix (29 recurrent and 7 in the advanced stage) by cytotoxic drugs was presented (Roy, 1967). Further studies have been made on another group of 33 cases by these drugs, making a total of 69 cases treated so far. In this article an assessment of results of treatment by cytotoxic drugs on these 69 cases has been made.

*Material and Methods*

Sixty-nine cases of carcinoma of the cervix were treated by cytotoxic drugs in Chittaranjan Cancer Hospital during the period of April '63 to June '69. Of these, 15 were in an advanced stage of the disease (14 in stage IV and 1 in stage III with involvement of whole of the vagina and parametria). In all these advanced cases treatment by any conventional form was not possible. The remaining 54 cases were recurrent. In the recurrent group, 14 were operated, in 12 of which external radiation was also given. The remaining 40 cases were treated by radium and external radiation. In this recurrent group, the disease recurred within the first year of treatment in 41 cases, within two years in 7 cases, within 3 years in 4 cases and above five years in 2 cases.

All cases in the advanced group were of epidermoid carcinomas. In the recurrent group, 47 were epidermoid carcinomas, 2 adenocarcinomas and 3 anaplastic carcinomas. In 2 cases no report was available.

*Drugs used*

In the initial stage of this stu
only one variety of drug was
But later on drugs were used i
bination with the available
ties in the market in o
avoid resistance to any one
some cases, when the co

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*Paper read at the 15th All-India Obstetric and Gynaecological Congress held at Margao, Goa, in December 1969.*

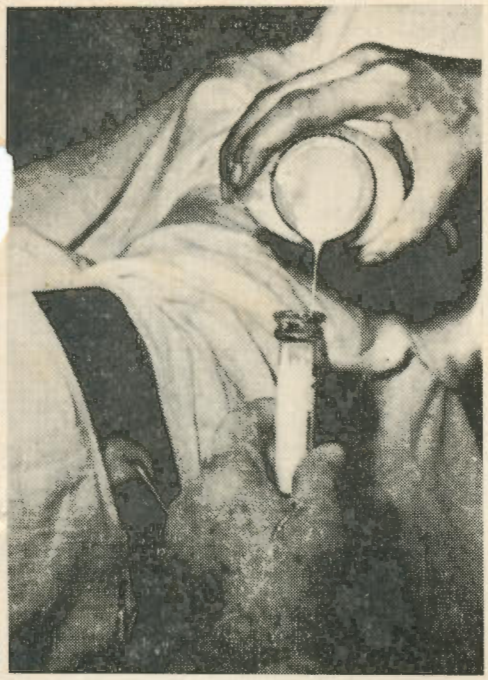

Fig. 1
Pouring the liquid plastic.

Fig. 2
Mixing the catalyst "M" 1/40 dilution in liquid paraffin half c.c. mixed for each 10 c.c. of liquid plastic in the syringe.

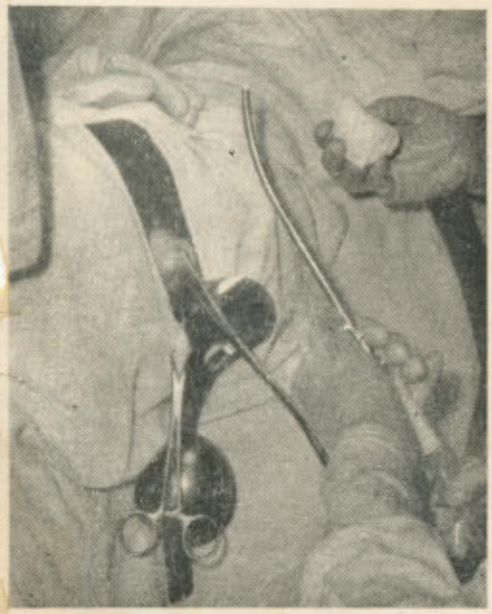

Fig. 3
Filling up of the canula upto the tip to record reading at the syringe for deciding correct amount introduced.

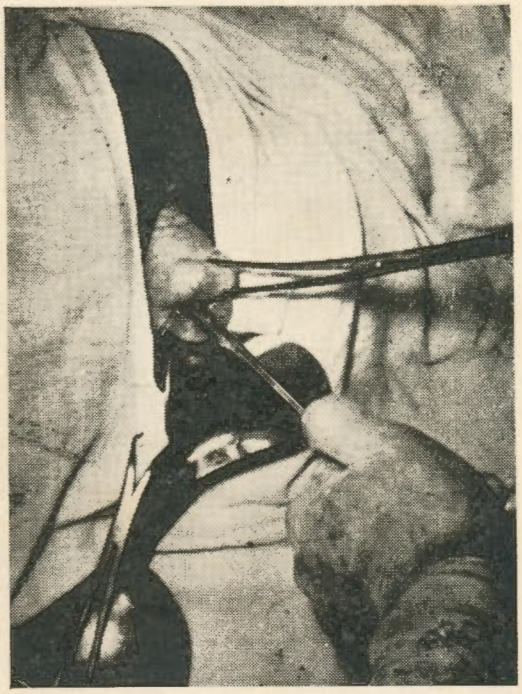

Fig. 4
Instillation through the cervix.

Fig. 5
White plastic seen near ampullary end of tube in a case of hysterectomy.

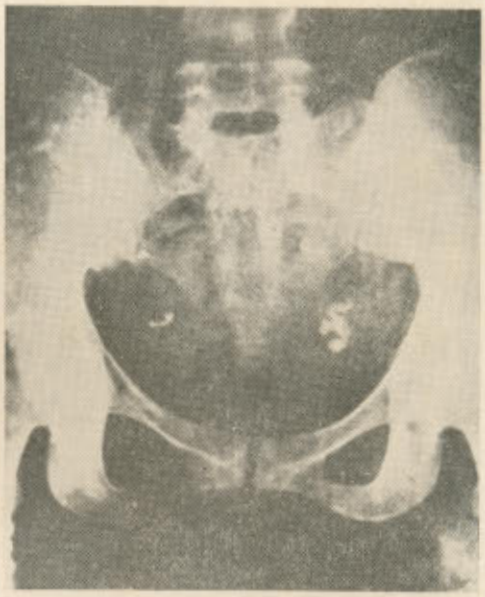

Fig. 6a
X'ray picture showing plastic material within tube.

Fig. 6b
X'ray picture of same patient after eleven months.

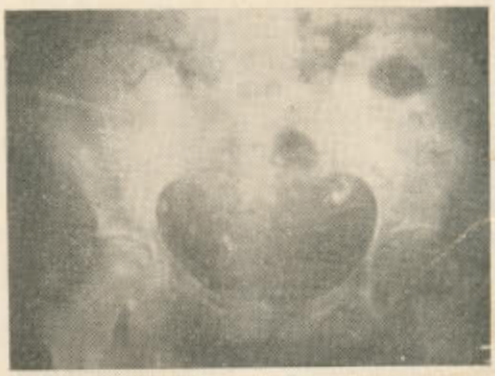

Fig. 7a
X'ray picture of another patient showing plastic in the tube.

Fig. 7b
X'ray picture of same patient after fifteen months.

Fig. 8
Plastic projecting through excised human fallopian tube demonstrating possibility of reversion.

*Endometriosis in Abdominal Scars Following Caesarean Section—Srivastava Et Al pp. 663-665*

Fig. 1.
...aph showing in'ands of endometrial ...is caesarean scar (H & E x 50).

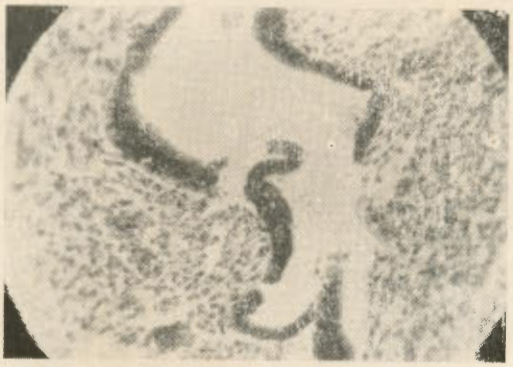

Fig. 2.
Photomicrograph showing nonsecretory columnar epithelium of the endometrial gland surrounded by stromal cells (H & E x 200).

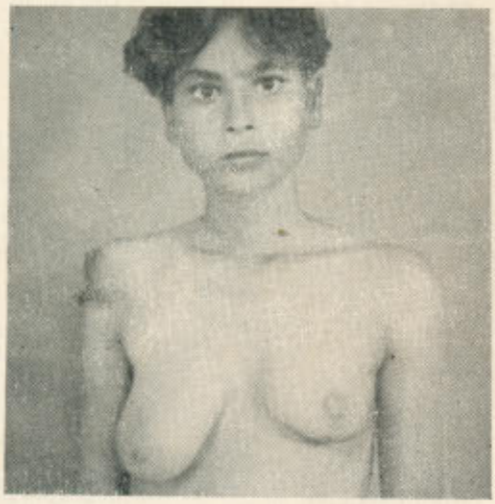

Fig. 1
Testicular feminization (Case No. 1). Note the feminine phenotypeic appearance. Beard and mustache are absent. Breasts are well developed.

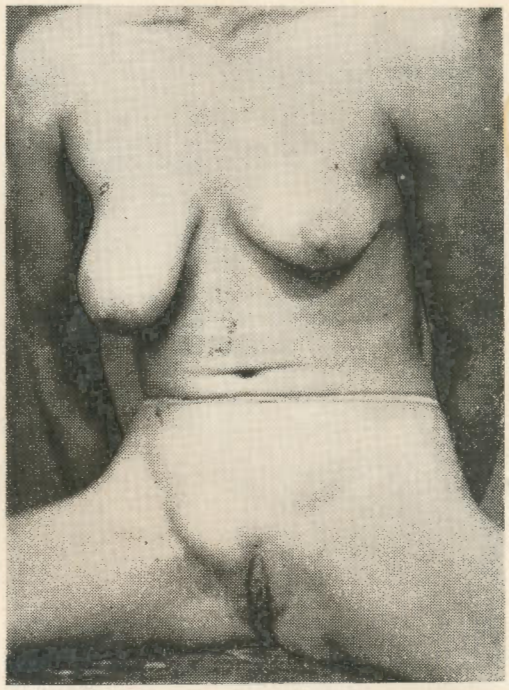

Fig. 2
Testicular feminization (Case No. 1). Note the well developed breasts and normal external genitalia, pubic hair is absent. Note the inguinal gonadal swelling.

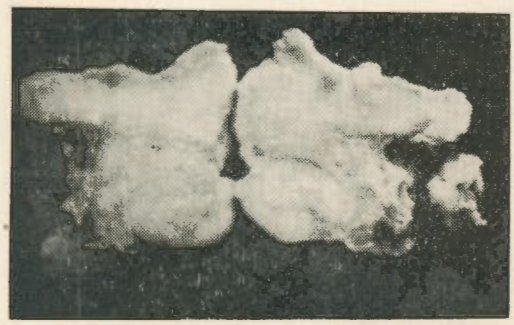

Fig. 3
Testicular feminization (case No. 1). Section of the gonad showing yellowish colouration.

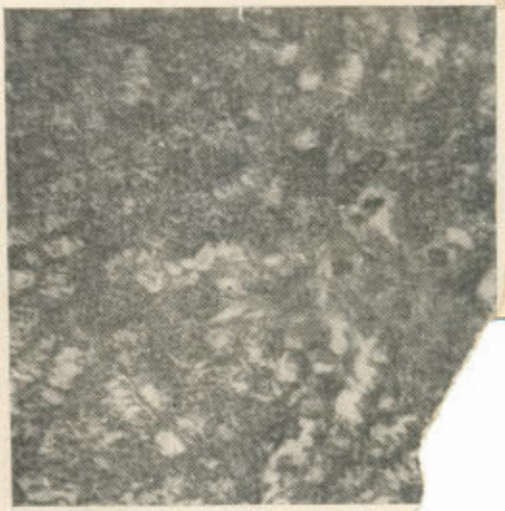

Fig. 4
Testicular feminization (case No. 1) gonad showing seminiferous tubule cells.

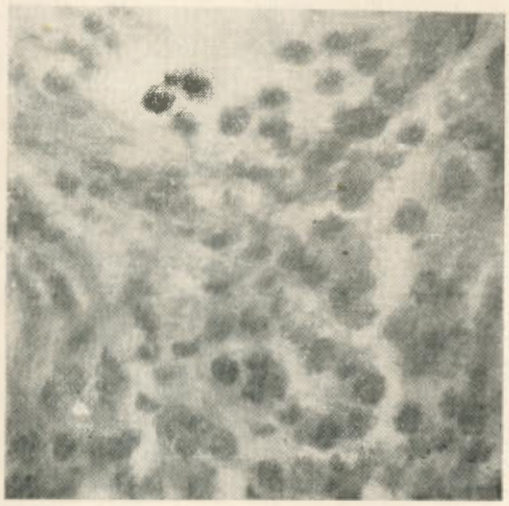

Fig. 5
Testicular feminization (case No. 1). High power. Note the seminiferous tubules and clusters of Leydig cells in between the tubules.

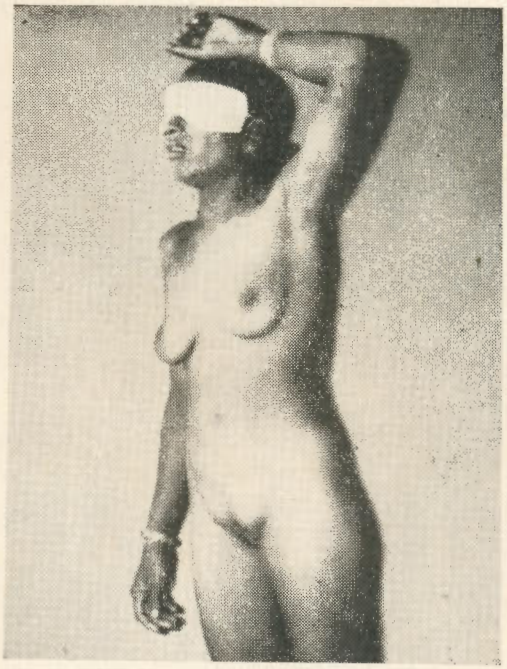

Fig. 6
Testicular feminization (case No. 2). Note the phenotype female with good breast development and normal external genitalia. Pubic and axillary hair are absent. Note also the absence of hair over the chin and upper lip.

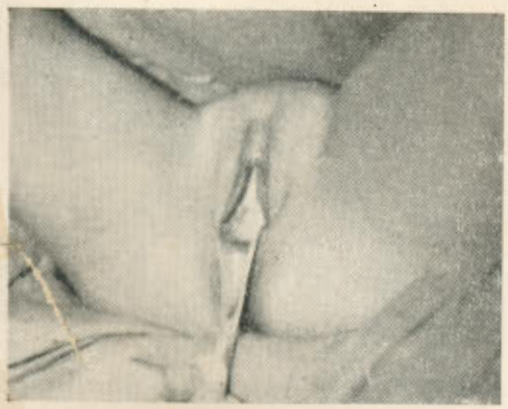

Fig. 7
Testicular feminization (case No. 2). Note the absence of pubic hair and normal female external genitalia. The speculum in the vagina shows the depth of the vagina.

*Portal Hypertension in Pregnancy—Gupta pp.* 612-617

Fig. 1, case 2—Barium Swallow AP lateral view showing oesophageal varices.

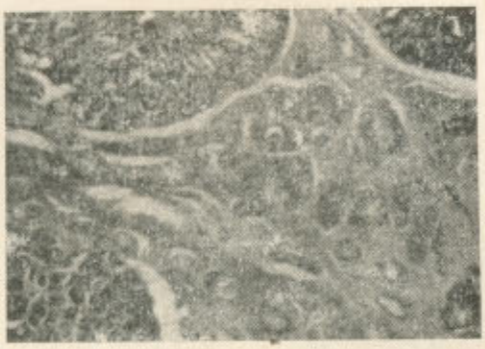

Fig. 1.
Microphotograph shows seminiferous tubules with lining Sertoli cells and germ cells. Note the absence of mature sperms (incomplete spermatogenic activity (H & E x 400).

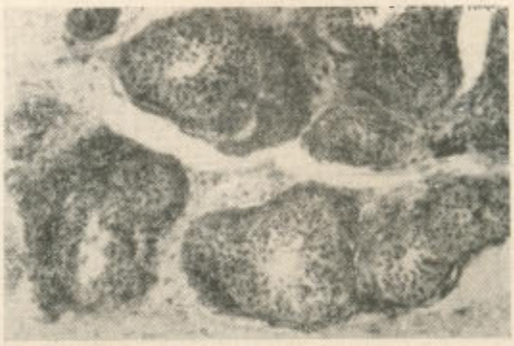

Fig. 2.
Microphotograph shows groups of immature Leydig cells enclosing one or two tubules (H E x 400).

Fig. 3.
Microphotograph shows seminiferous tubules surrounded by groups of Leydig cells (H & E x 100).

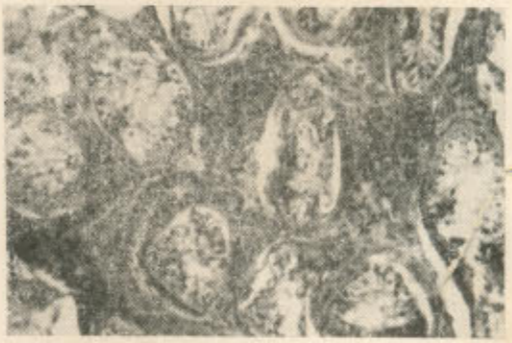

Fig. 4.
Microphotograph shows seminiferous tubules surrounded by immature Leydig cells. The former is lined by immature Sertoli cells. No germ cells are seen (H & E x 400).

SCAR ENDOMETRIOSIS — I

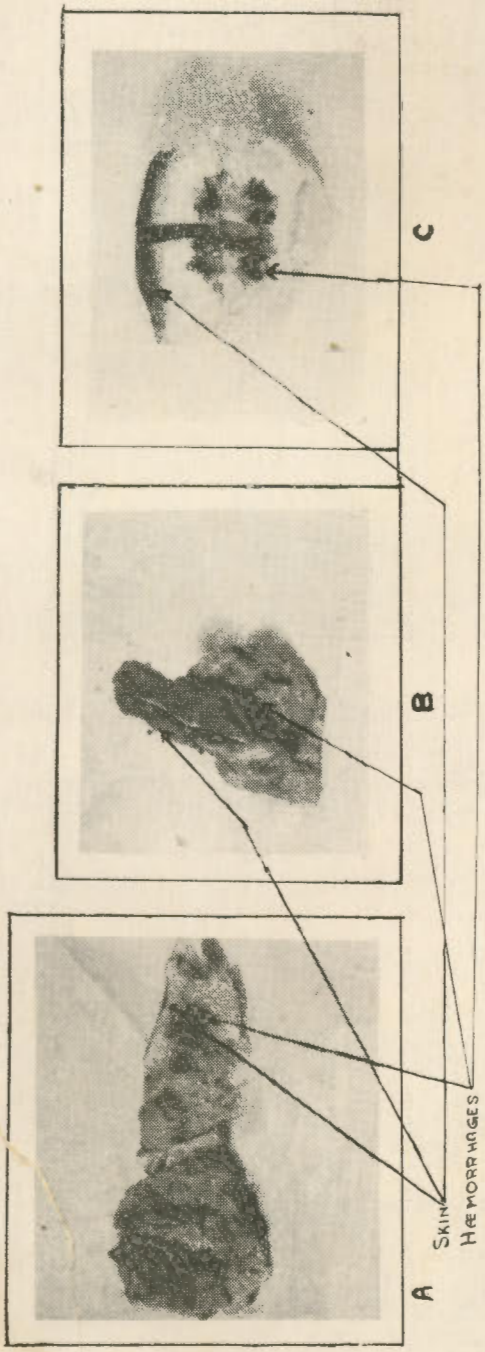


FIG.-I *

Fig. 1 (a), (b) & (c)—Macroscopic section showing area of haemorrhages underneath the abdominal scar tissue.

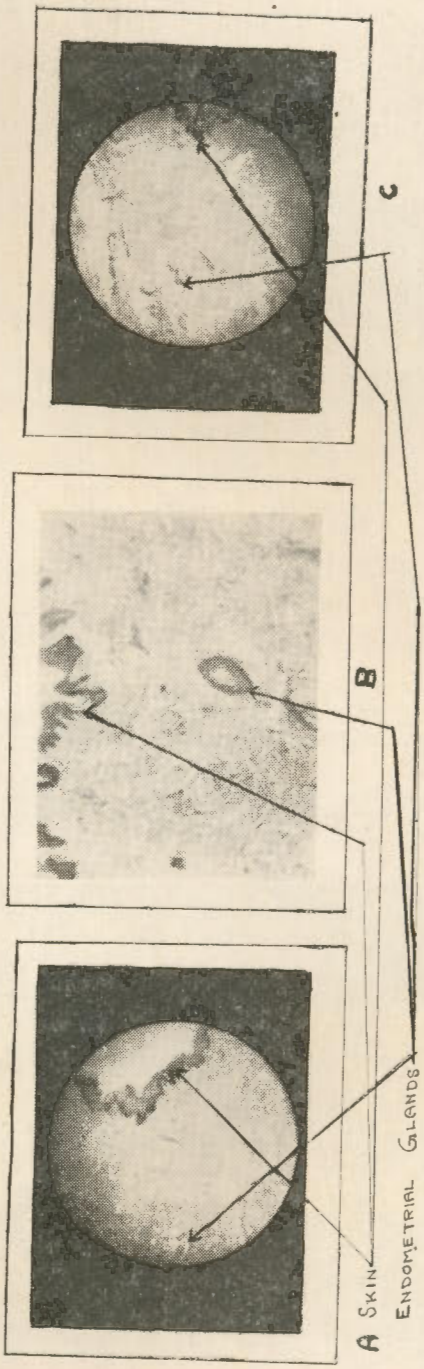


FIG – II ✱

Fig. 2 (a), (b) & (c)—Microphotographs of the operated specimen showing endometrial glands and skin tissue.

*Rupture of the Uterus and the Urinary Bladder*
*—Parikh & Shah pp.* 666-667

Fig. 1.
Schematic diagram showing the rupture of the uterus and the urinary bladder with the escape of the foetal head and the hand with a part of the trunk into the bladder.

*Pregnancy in Rudimentary Horn of the Uterus*
*—Jacob & Bhargava pp.* 668-672

Fig. 1.
Showing the foetus and the excised rudimentary horn.

*Primary Carcinoma of the Fallopian Tube—Daruvala pp.* 679-681

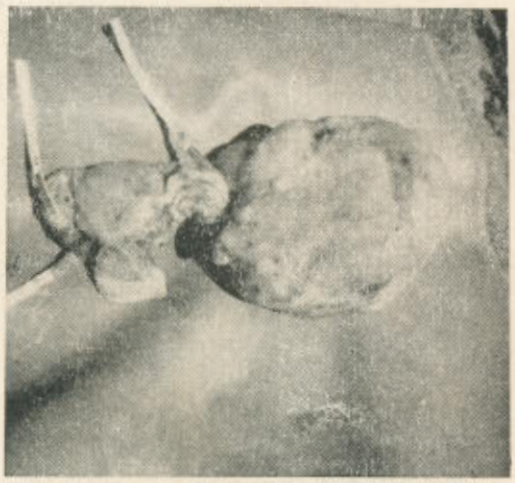

Fig. 1
Gross pathology showing tumour mass on the right side and separate ovaries.

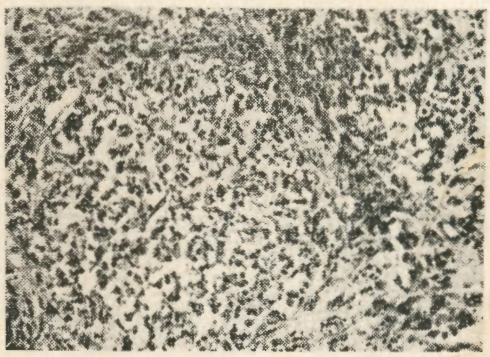

Fig. 2
Grade III alveolar medullary carcinoma of the fallopian tube. H.P.

Fig. 1.
Showing conjoint twins with four upper extremities, four lower extremities, fusion from the head to the upper part of the abdomen upto the umbilicus and two separate pelveses.

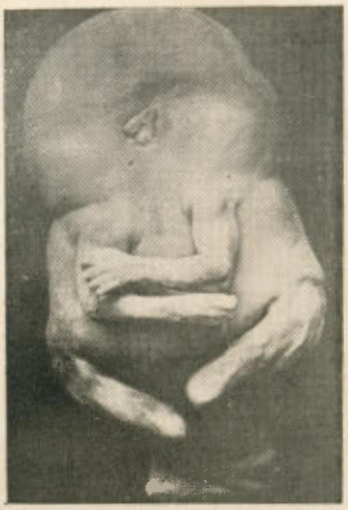

Fig. 2.
Showing big gap in the anterior abdominal wall where the umbilicus was attached.

Fig. 3.
Showing one pair of ears at the back very close to each other.

Fig. 4.
Showing placenta with attached cord and its blood vessels.

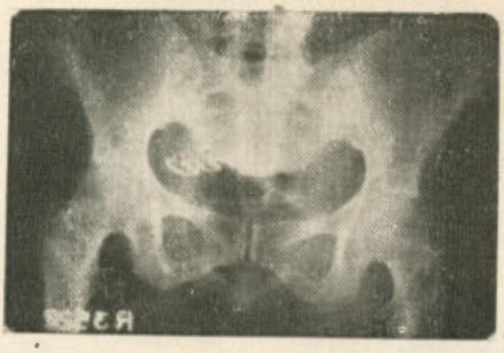

Fig. 1.
Showing transverse disposition of the loop on right side away from midline.

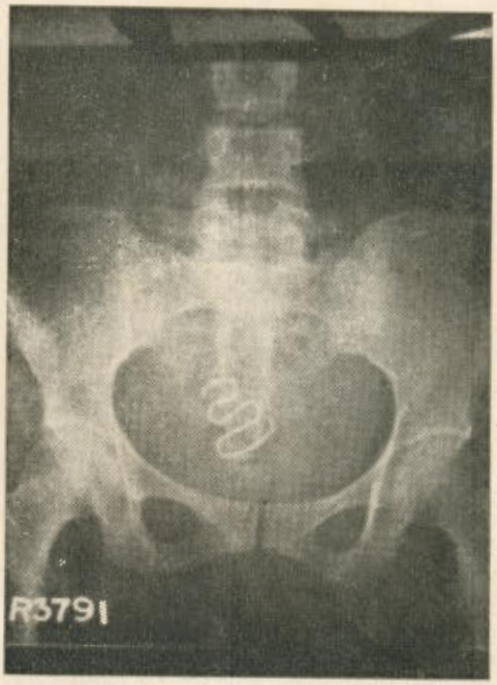


Fig. 2.
Showing vertical disposition of the loop on right side away from midline.

Fig. 3a.
Loop in situ with part of the right tube removed by partial salpingectomy (anterior aspect).

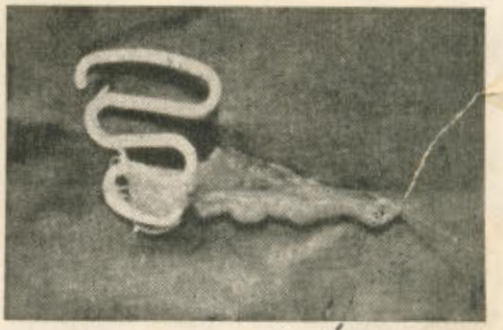

Fig. 3b.
Loop in situ with part of the right tube removed by partial salpingectomy (posterior aspect).

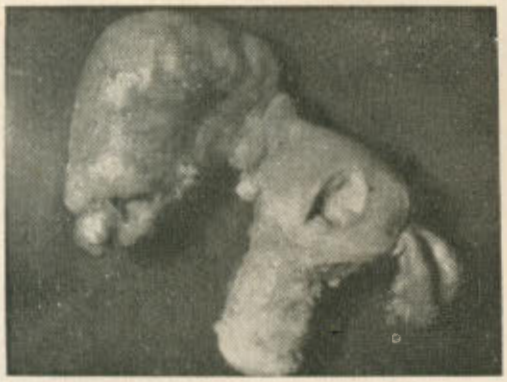

Fig. 1.
Photograph showing uterus. malignant tumour of the right fallopian tube, the left normal tube and ovary.

Fig. 2.
Posterior view of the specimen showing invasion of the external surface of the right ovary by the carcinoma of the right fallopian tube.

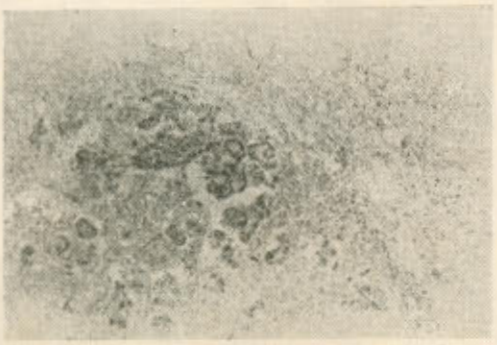

Fig. 3.
Microphotograph showing adeno-carcinoma having a papillary alveolar arrangement.

*Stromatosis—Aron & Pasricha pp—686-688*

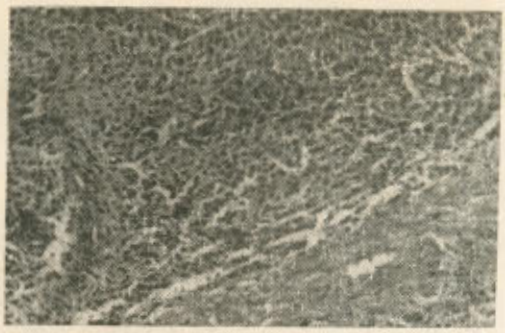

Fig. 1
Low power microphotograph of section of the uterine wall showing stromatosis.

*Stromatosis—Aron & Pasricha pp—686-688*

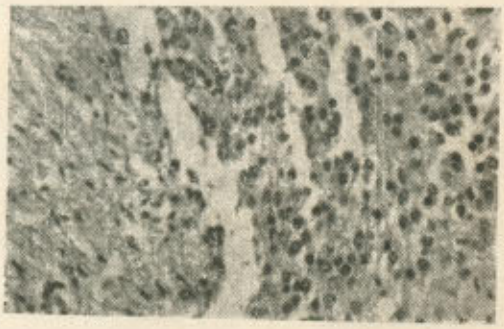

Fig. 2
High power microphotograph of section through uterine wall showing stromatosis.

*Adenofibroma of the Ovary—Srivastava & Mal pp. 689-690*

Fig. 1.
Gross-cut surface of the large ovarian tumour showing nodular appearance.

Fig. 2
Photomicrograph showing whorled appearance of connective tissue stroma interspersed with several tubular glands (H & E x 50).

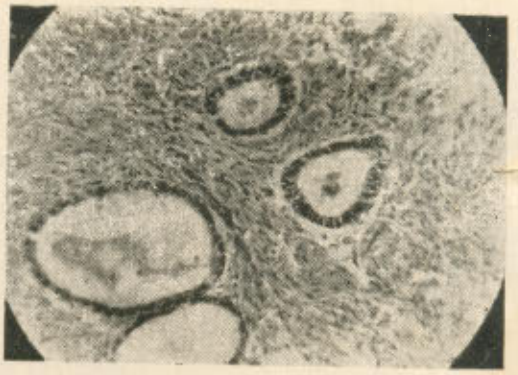

Fig. 3
Photomicrograph showing tubular glands lined by cuboidal epithelium. The stromal cells are spindle shaped (H & E x 200).

group of drugs had failed to relieve their sufferings, other available varieties were used.

In Table I, the list of drugs used in this series is given.

TABLE 1
*Varieties of Drugs used*

| Varieties | No. of Cases |
|---|---|
| Single— | |
| 1. Methotrexate .. .. | 29 |
| 2. Endoxan (Cyclophosphamide) | 11 |
| Combination— | |
| 1. Methotrexate and Endoxan | 16 |
| 2. Endoxan and Leukeran (Chlorambucil) .. .. | 2 |
| 3. Mitomycin and Endoxan .. | 1 |
| 4. Methotrexate, Endoxan and Leukeran or Thio-Tepa .. | 8 |
| 5. Methotrexate, Endoxan, Leukeran and Mitomycin or Velbe .. .. .. | 2 |
| Total .. | 69 |

The drugs were used through the oral, intramuscular, intravenous routes and also by local injections. In 2 cases the drugs were used through the intra-arterial routes via the uterine arteries. As the administration of drugs through the intra-arterial route produced severe reactions, this route is not favoured.

*Special Investigation*

As described in my previous papers, haematological examinations for Hb%, total WBC and platelet count were routinely done, both before and after each course of drugs. Vaginal smear examinations and biopsies were done routinely.

*Subjective symptoms and their response to treatment*

In both advanced and recurrent group, there were more than one presenting symptom. Bleeding and discharge were more common in advanced group whereas pain was the outstanding symptom in the recurrent group. In Table 2 subjective symptoms of both groups have been shown as well as their response to the drugs:

In the recurrent group 2 patients were asymptomatic. Subjective response could not be assessed in 5 cases, one of which was lost sight of and in the other 4 sufficient amount of drugs could not be administered.

Subjective response has been noted under two categories — permanent and temporary. Permanent relief is one where the symptoms did not recur even after stopping the drugs

TABLE II
*Subjective symptoms and their response to treatment*

| Symptoms | RECURRENT | | | | ADVANCED | | | |
|---|---|---|---|---|---|---|---|---|
| | No. of cases | Permanent relief | Temporary relief | No. relief | No. of cases | Permanent relief | Temporary relief | No. relief |
| Pain | 42 | 19 | 7 | 11 | 10 | 9 | - | 1 |
| Bleeding | 18 | 10 | 4 | 3 | 15 | 14 | - | 1 |
| Discharge | 17 | 7 | 4 | 5 | 14 | 11 | - | 3 |
| Dysuria | 3 | 1 | - | 1 | - | - | - | - |
| Proctitis | 3 | - | - | 1 | - | - | - | - |
| Miscellaneous | 6 | 1 | - | 5 | - | - | - | - |

whereas in the temporary group, symptoms subsided for some period of time but again recurred even while treatment was going on.

From the above table it could be seen that relief of symptoms was obtained in both groups, but more in advanced ones.

*Objective response*

As described by Masterson and Nelson (1965) the objective response has been evaluated under three terminologies such as regression, arrest and progression. Table 3 shows the objective response of this group of cases by cytotoxic drugs.

From the above table it can be seen that regression of tumour was noted in 5 cases of recurrent group and 3 cases of advanced ones. Regression was more marked in the advanced group (20%) than in the recurrent ones (9.2%). Probably radiation by producing fibrosis may be responsible for interfering with the action of drugs in the recurrent group. A brief summary of cases where the tumour regressed has been given in Table 4.

TABLE III

*Objective response to treatment*

| Type | No. of cases | Regression | Arrest | Progression | Not assessable |
|---|---|---|---|---|---|
| Recurrent | 54 | 5 | 7 | 33 | 9 |
| Advanced | 15 | 3 | 2 | 8 | 2 |

TABLE IV

*Brief summary of cases of Regression*

| Reg. No. | Findings | Treatment | Survival |
|---|---|---|---|
| RECURRENT: | | | |
| 1.61/5170 | Ca cervix I. Lymphadenectomy on 17.3.62 followed by 3 rad. & ext. radia. Recurrence of growth 1 year after treatment. | 1. Methotrexate —325 mg.<br>2. Endoxan— 15 gr. | Irregular in attendance. Did not turn up for 1 yr. after treatment. Died in 35th month. |
| 2.65/2124 | Ca Cervix III. Had 3 rad. & ext. radiation completed on 26.7.65. After 8 mths. rectum was infiltrated by the growth. | 1. Methotrexate— 60 mg. by Intra-arterial route.<br>2. Endoxan—2 gm. | Pt. living for 3½ yrs. without any symptoms. |
| 3.66/506 | Ca cervix III. Had 3 rad. & ext. radiation on 18.4.66. Growth was persistent. | 1. Methotreate —500 mg.<br>2. Endox—2 gm.<br>3. Leukeran —120 mg. | Subj. & objective response noted. When treatment stopped for 6 mths. growth recur. and died in 18th mth. of treatment. |

| Reg. No. | Findings | Treatment | Survival |
|---|---|---|---|
| 4.58/1541 | Ca cervix III. Had 3 rad. & ext. rad. in 1958. After 8 yrs. metas. in left lung with haemoptysis, dyspnoea & pain in chest. | 1. Methotrexate —500 gm. | Subj. response noted. Mass regressed partially. After stopping drugs for 6 mths. symp. recurred Lobectomy done. Living for 3 yrs. |
| 5.65/5703 | Ca Cervix III. Had 3 rad. & rad. on 23.2.66. After 2 years Inguinal metastases — 4.5 cm x 2.5 cm. | 1. Methotrexate —250 mg.<br>2. Endoxan —2.5 gm. | Mass completely disappeared. Living & without any symptoms for 18 months. |
| ADVANCED | | | |
| 1.64/4521 | Ca Cervix III with involvement of whole of vagina & parametria. | Methotrexate —300 mg. | Growth regressed. Did not turn up for 6 months. Growth recurred & died in 24th month of treatment. |
| 2.65/4311 | Ca Cervix IV with involvement of bladder and metastatic nodule around urethra. | 1. Methotr. —25.0 mg.<br>2. Endoxan—6 gm.<br>3. Leukeran—200 mg. | Tumour regressed & then treated by 3 rad. & ext. rad. After 1 year metastatic nodule around urethra. Drugs started. No response. Died in 22nd month of treatment. |
| 3.66/4118 | Ca Cervix IV with involvement of rectum. | 1. Methotr.—25.0 mg<br>2. Endoxan—5 gm.<br>3. Leukeran—200 mg. | Tumour regressed & then treated by 3 rad. & ext. rad. Growth recurred again. Subj. & obj. responses noted. Living & completed 3 years of treatment. |

There was arrest of progress of tumour in 7 cases in the recurrent group and in 2 cases in the advanced ones. It is interesting to note that though there was arrest of progress of tumour, malignant cells were found on repeated smear examinations in 4 cases of the recurrent group even though they had a sufficient amount of cytotoxic drugs. One of them died in the eighth month of treatment, one in the twelfth month, one in the fifteenth month and another in the twenty-fourth month.

In both cases of the arrested group in the advanced series, malignant cells disappeared and the cases were subsequently treated by radium and external radiation. The tumour recurred later on in both of them and cytotoxic drugs were again administered but with no result. Both of them died in the 15th month of treatment.

*Complications of therapy*

It is well known that cytotoxic drugs are very toxic and this is revealed in Table V.

Out of 5 unassessable cases in methotrexate series, 4 had subjective relief of symptoms and in endoxan series, 2 had relief of symptoms.

TABLE V
*Complications of Therapy*

| | Nausea & Vom. | Stomatitis. | Dermatitis | Alopecia | Diarrhoea | Blood Changes Fall | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Hb% | W.B.C. | Platelet |
| Recurrent | 31 | 28 | 20 | 3 | 17 | 19 | 16 | 5 |
| Advanced | 7 | 10 | 9 | - | 3 | 9 | 5 | 4 |

In only 4 cases no toxicity was observed but in the rest toxic manifestation of some form was noted.

Out of 69 cases, Hb percentage fell in 28 cases. In some of them it fell by about 25 to 30 per cent, more especially when the drugs were administered through the intra-arterial route as mentioned in my previous paper W.B.C. count also fell in 21 cases and in one of them upto 1200 per c.m.m. Blood transfusion had to be given in many of these cases.

*Results of Therapy*

In Table VI, an assessment of results by the drugs both used singly or in combination, has been made.

From the above table it could be seen that the subjective response was noted in 69 per cent of cases in methotrexate series (20 out of 29 cases) and 54.5 per cent in endoxan series (6 out of 11 cases); whereas subjective relief was obtained more in double combination (17 out of 19 cases, 89 per cent) and multiple combination (9 out of 10 cases, 90 per cent). In all subjective relief was obtained in about 75.3 per cent of cases (52 out of 69 cases).

As regards the objective response, regression of tumour was noted more in double (21 per cent) and multiple combination (20 per cent) than methotrexate alone (7 per cent).

TABLE VI
*Results of Therapy*

| Drugs | Symp. relieved & grow. regressed | Symp. relieved & growth arrest | Symp. relieved & growth progression | No relief but progression | Not Assessable |
|---|---|---|---|---|---|
| Methotrexate (29 cases) | 2 | 3 | 11 | 8 | 5 |
| Endoxan (11 cases) | - | - | 4 | 2 | 5 |
| Double Combination (19 cases) | 4 | 1 | 12 | 1 | 1 |
| Multiple Combination (10 cases) | 2 | 5 | 2 | 1 | - |

Arrest of progress of tumour was noted more in multiple combination (5 out of 10 cases) than in others. Neither regression nor arrest of tumour was observed in endoxan administered cases.

*Salvage rate*

Out of 8 patients in regression group, 4 are living (3 more than 3 years and 1 for 18 months) and the rest died (3 within 2 years and 1 in 35th month of treatment).

In arrested group one patient is living for 9 months, one was lost sight of after 10 months of treatment and 7 died (2 died within 1 year, 4 within 2 years and 1 in 31st month of treatment).

In the remaining 52 cases where the disease progressed in spite of treatment, 38 died within 1 year and 3 within 2 years. Eleven patients were unfortunately lost sight of.

Considering that only 5 patients are surviving out of this small series of 69 cases, a conclusion may be drawn that cytotoxic drugs do not improve the salvage rate of these groups of patients.

*Discussion*

In the advanced cases of carcinoma of the cervix as well as in the recurrent group, there is practically no treatment at all and these patients are often allowed to wait for a miserable and painful death. Cytotoxic drugs have been tried in these cases. Subjective relief has been obtained by these drugs in 75.3 per cent of cases (52 out of 69 cases).

So far as the objective response is concerned, the success rate is not so much. In only 8 cases regression of the tumour was noted (11.6 per cent). Even in this regression group, 50 per cent of patients died within 3 years. In 9 cases arrest of progress of tumour was noted for some time but 7 of them died within 3 years. Moreover, it was observed that cytotoxic drugs have not been able to improve the salvage rate of these groups of cases.

From this small series it may be concluded that cytotoxic drugs may be used as a palliative measure in advanced cases of carcinoma of the cervix as well as in the recurrent group to relieve their sufferings, and this seems to be of definite benefit. Occasionally, regression of tumour may be noted by the use of these drugs. But these drugs are rather expensive and toxic and the main problems are which variety of drugs to be used and how long the treatment should be continued. In this series, the use of combination group of drugs produced more subjective and objective responses.

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