METRONIDAZOLE AS A CHEMICAL RADIOSENSITIZER IN THE TREATMENT OF ADVANCED CERVICAL MALIGNANCY, DOUBLE BLIND TRIAL OF METRONIDAZOLE

by

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SUMMARY

A double blind clinical trial of Metronidazole and placebo was conducted on 80 patients of cancer cervix stage III B between the age group of 30 to 60 years to evaluate the selective response of malignant tumours to irradiation following radio-sensitization of the hypoxic cells.

Introduction

Carcinoma of the cervix is one of the leading causes of death among young women in our country. Regretably 75% of all cancer patients are stage III or IV at initial presentation with poor response when treated by the conventional forms of radiation. This failure is currently attributed to the presence of radioresistant hypoxic cells in the tumour mass. To circumvent this, Metronidazole as a chemical radiosensitizer of the hypoxic cells can be effectively used, has been reported by Mogre *et al.*

The classic work of L. H. Gray and his colleagues demonstrated the importance of hypoxic cells in the radioresistance and the use of Metronidazole which acts in 'oxygen' like manner when administered before irradiation, with little or no effect upon well oxygenated normal cells.

From: Govt. Medical College and Hospital, Nagpur.

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Material and Methods

This study was carried out as a double blind clinical trial. The patients were divided in:

Group A: Who were administered Tab. Metrogyl.

Group B: Who were administered placebo.

The patients were alternately selected for A and B therapy. All patients selected for the study were Stage III with large growths, where the os was not negotiated or Visualized. Initially the therapy was started in the dose of 400 mg three times a day which was gradually increased to 800 mg and subsequently a single dose of 2 : 4 gms 4 hours before the radiation treatment. Tablet Stemetil 10 mg was administered one hour before the drug therapy. All patients received Low Energy Transfer Gamma Irradiation 200 rads per day for five days a week. Total dose 5000 to 6000 rads was given. The patients were given anabolic steroids and supportive therapy

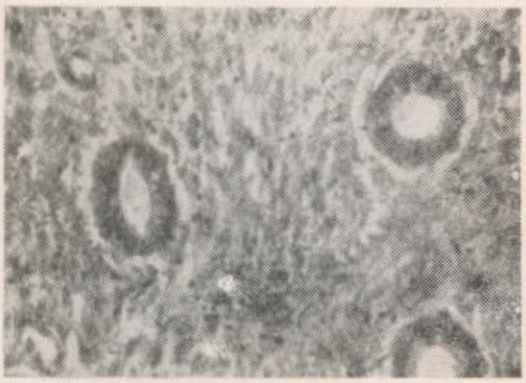

Fig. 1
Microphotograph showing haemorrhagic change of endometrium with oedema of stroma.

Fig. 2
Microphotograph showing collazinisation of major part of endometrium.

Fig. 3
Microphotograph showing papillary changes of surface epithelium of endometrial glands.

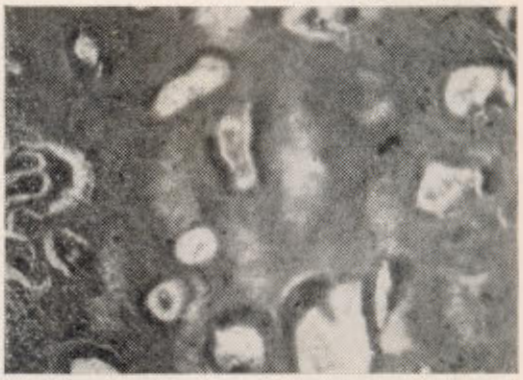

Fig. 4
Microphotograph showing glandular atrophy.

Endometrial Cytology as a Screening Procedure—Neeraj Goel et al pp. 133-138

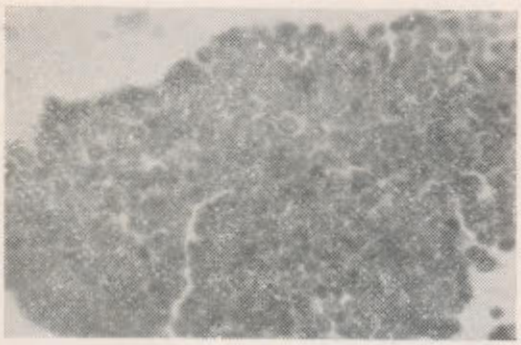

Fig. 1
Endometrial hyperplasia on cytological examination.

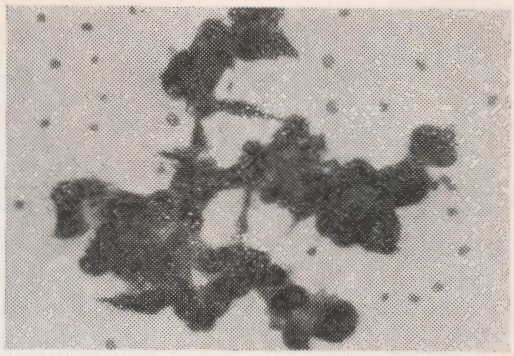

Fig. 2
Showing malignant cells from endometrial cytological aspirate.

Kleeblattschadel Syndrome—Chaturvedi et al pp. 178-179

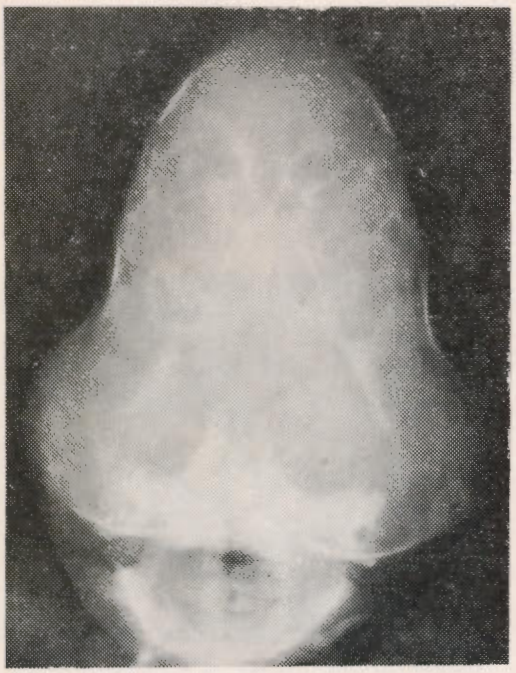

Fig. 1
X-ray skull A.P. view showing trilobed skull.

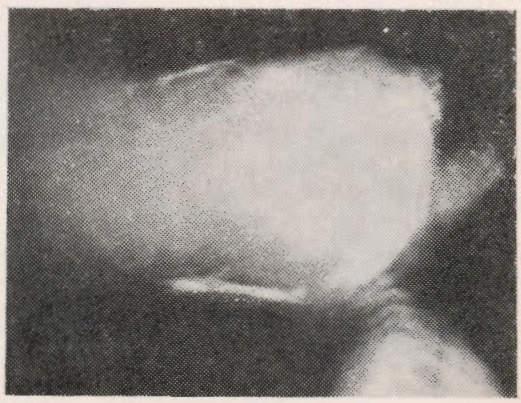

Fig. 2
X-ray lateral view of trilobed skull.

Endometrial Sinus Tumour of Ovary—Kirpal Kaur et al p. 173

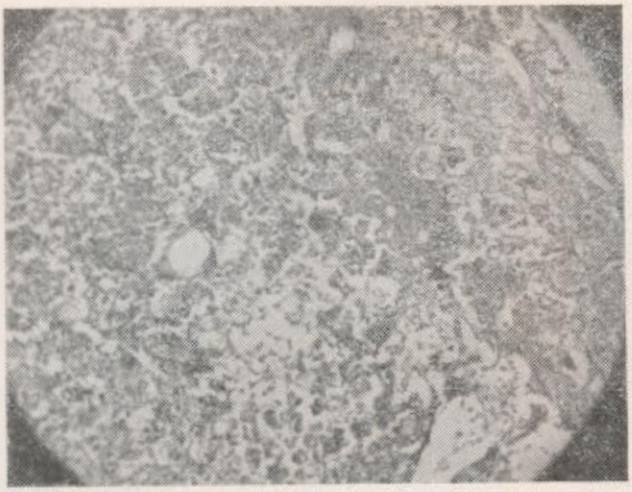

Fig. 1
Photomicrograph of endo-dermal sinus tumour showing loose vacuolated network of irregular embryonal cells with communication channels.

Hydatiform Mole with Coexistent Foetus Goswami p. 174

Fig. 1
Shows partial molar degenerations of a single placenta with a coexistent foetus.

An Obstetric Emergency—Mendelson's Syndrome —Preruna Panchal p. 181

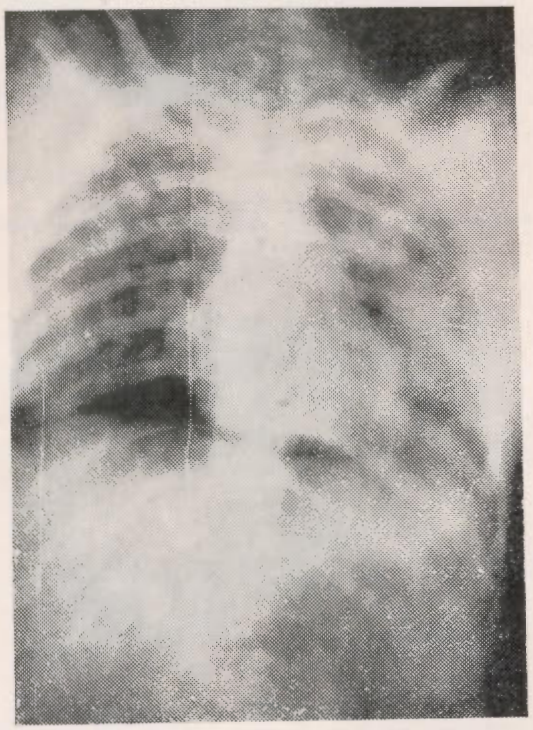

Fig. 1
Massive congestion with consolidation.

An Unusual Combination of Tubal and Cornual Pregnancy—Mishra et al p. 183

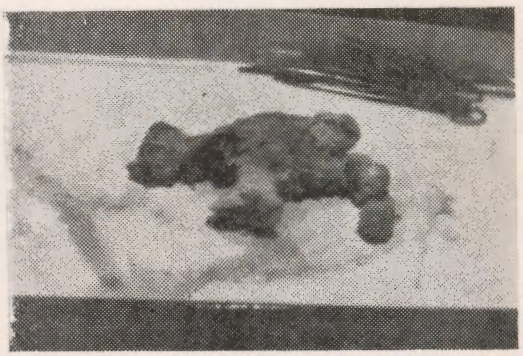

Fig. 1
Specimen of uterus. The cornual sac is seen.

Cervical Tuberculosis Simulating Cancer Cervix—Panchal & Kapadia pp. 186-187

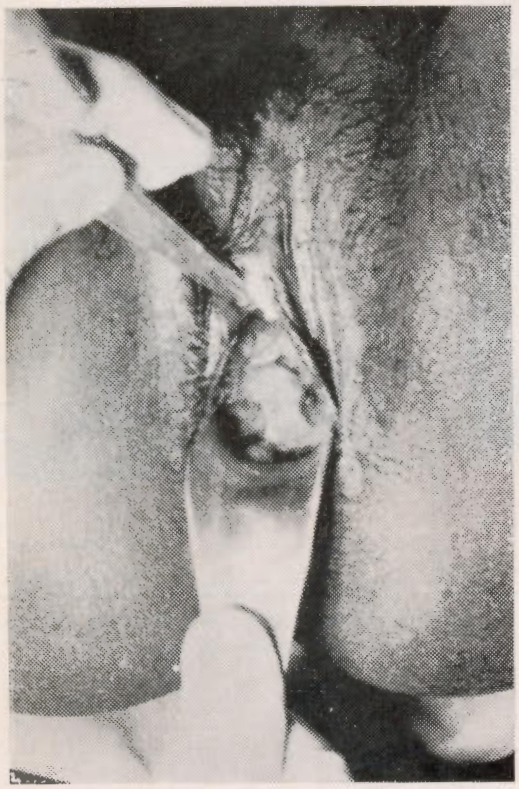

Fig. 1
Showing Cauliflower growth on cervix.

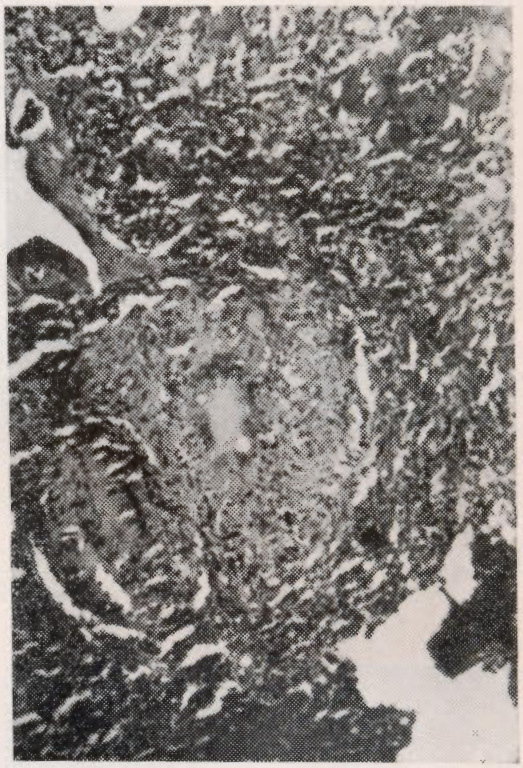

Fig. 2
Showing histopathology of typical tuberculous granuloma.

Bilateral Tubal Pregnancy—Mishra & Jha p. 184

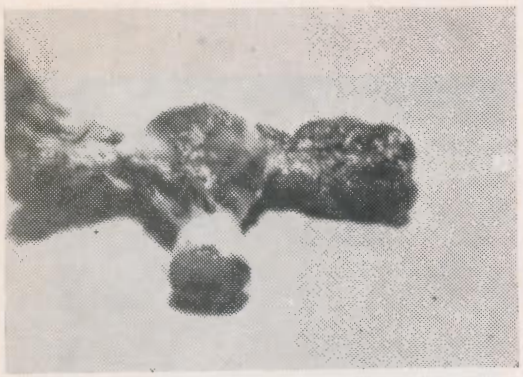

Fig. 1
Specimen showing uterus and bilateral tubal pregnancy.

Choriocarcinoma with Metastasis in Vagina—Rao et al pp. 188-189

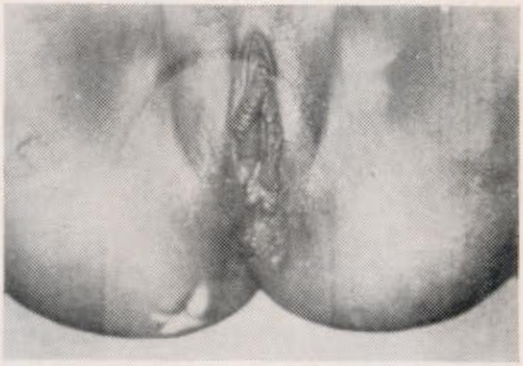

Fig. 1
Cruciate incision through which the ischio-rectal fossa abscess was drained.

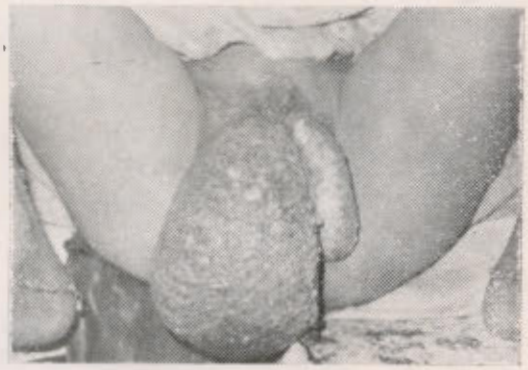

Fig. 1
Condyloma lata.

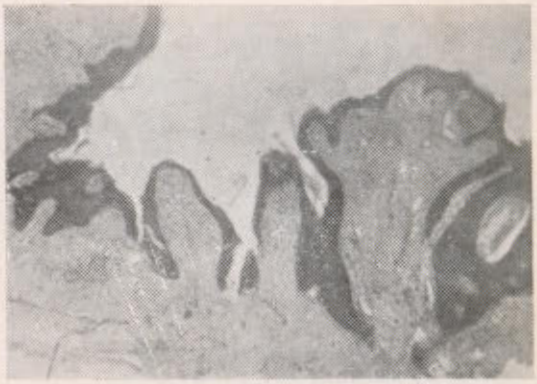

Fig. 2
Condyloma lata histological picture.

Fig. 3
Condyloma lata histological picture.

Fig. 4
Bowen's disease of vulva.

Fig. 5
Histological picture of Bowen's disease of vulva.

Fig. 6
Histopathological picture of Bowen's disease.

Fig. 7
Histopathological picture of atrophic leukoplakia.

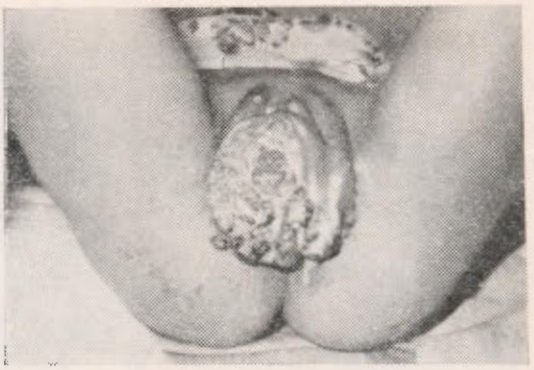

Fig. 8
Condyloma accuminata (giant condyloma).

Four Unusual Vulval Cases—N. Malhotra et al pp. 190-192

Fig. 9
Histopathology features of condylome accumanata.

An Unusual Presentation of Krukenberg's Tumour of the Ovary—Narvekar & Joglekar p. 199

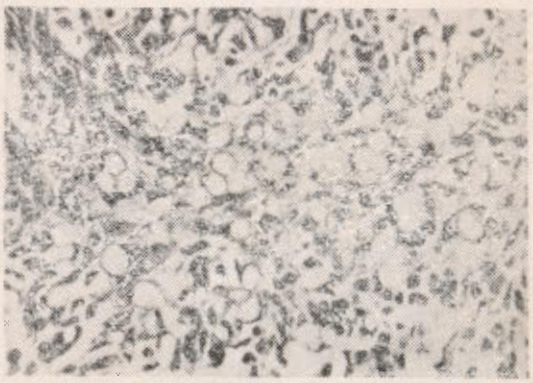

Fig. 1
Histology of Krukenberg tumour.

Rohitansky-Kuster-Hauser Syndrome—Deshpande & Lele p. 200

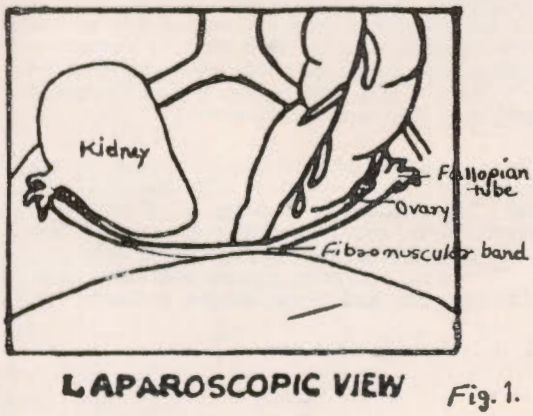

Fig. 1
Laparoscopic view showing mullarian dysgenesis and pelvic lump.

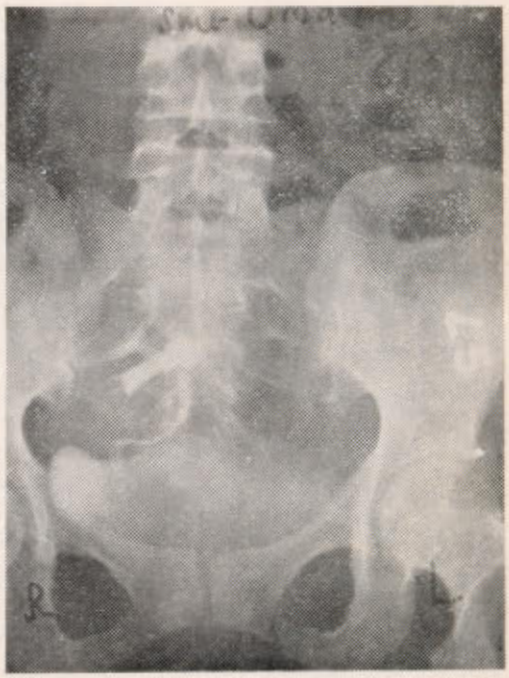

Fig. 2
I.V.P. showing single functioning pelvic kidney.

The Indian College of Obstetricians and Gynaecologists

of

The Federation of Obstetrics and Gynaecological Societies of India

Purandare Griha, 31/C, Dr. N. A. Purandare Marg, Bombay 400 007

Indian College of Obstetricians and Gynaccologist established on 21st December 1984, has made quite a great impetus. We have now 180 Founder Fellows. The next convocation to confer the Fellowship will be held in Ahmedabad, Gujarat, at the time of The 30th All India Obstetric and Gynaecological Congress in December 1986.

The College will hold the next National Seminar at Calcutta. It was unfortunate that Dr. Vegadasalam could not come from Singapore to Calcutta due to some local problems as conveyed by him. And hence this Seminar was postponed. We appeal to all our Senior Colleagues to be fellows of the Indian College of Obstetricians and Gynaecologists.

The requirements for application are that the Federation member must have aquired the Post Graduate qualification for 15 years as specified and a member of any National Society of Obstetrics and Gynaecology affiliated to the Federation of Obstetrics and Gynaecological Societies of India for 10 years. We have 85 Societies affiliated to the Federation and a membership of more than 6000 practising Obstetricians and Gynaecologists. We shall reach the list of 200 Founder Fellowship before June end 1986. I request all the Founder Fellows of College to write to me if they have still not received either the Fellowship Certificate or the Gold Plated Silver Memento. I request those Founder Fellows who have still not sent their fellowship forms by Registered post to send the same at the earliest.

Indian college of Obstetricians and Gynaecologists adhoce Committee will meet in June 1986 at Hubli when the Managing Committee of the Federation meets at the same time. I take this privilage to request all the members of the Federation for suggestions to be incorporated in the future academic activities of the college.

We will approach the Maharashtra State Government to allocate us a piece of land where we can build our 'HOUSE' for the Indian College of Obstetricians and Gynaecologists. The largest community of specialists practising in India and actively involved in the maternal and child Health care as well as the National Family Planning Programmes. The College will plan various Scientific and Social Programmes with an ultimate objective to serve the people of India in matters of various Family Planning outlays concerned with Medical and Surgical contraceptions and develop newer modalities which are safe effective economical and readily accepted. Our Ultimate aim is to achieve the Alma Ata commitments by 2000 A.D. I request to the readers to suggest some important topics for deleberations in he Scientific Programme of the 30th All India Obstetrics and Gynaecological Congress. This will be the Indian College of Obstetricians and Gynaecologists earmarked symposium at the annual conference.

You will be delighted to note that in 1984 The American Board of Obstetrics and Gynaecology certified about 1000 practising Obstetricians and Gynaecologists. In line with the British College of Obstetricians and Gynaecologist, The American College of Obstetricians and Gynaecologist, Australian and Newzealand Obstetricians and Gynaecologist, we will have our constitution and byelaws ready by the end of 1986. The college will unique in status and erst while activities, in this geographical region. We request for your support and cooperation in our efforts to build this prestigious citadel of Obstetricians and Gynaecologist of India.

For further information please contact Dr. C. L. Jhaveri, Chairman ICOG.

Dr. C. B. Purandare, Hon. General Secretary, FOGSI.	Dr. R. V. Bhatt, President, FOGSI.	Dr. C. L. Jhaveri, Chairman, ICOG.

during treatment. The response to therapy was assessed subjectively.

1. *Subjective* : Patients acceptability and tolerability of drug after 5 weeks.

2. *Objective* : Regression of the tumour at the end of 5 weeks, 3 months 6 months and one year which was graded as follows :

(a) Excellent : Almost complete regression of the tumour

(b) Good: 50 to 70% regression of the tumour

(c) Fair : 30 to 50% regression of the tumor.

(d) Nil : No response in regression of tumor.

Observations

Total Number of 80 patients were selected for the study. The results obtained after the treatment are given in Tables I and II.

TABLE I
Subjective Response

Tolerance	Group A	Group B
Good	16	26
Fair	23	14
Poor	1	0
Total	40	40

Four patients in Group A, 3 patients in Group B and 6 patients in Group A, 7 patients in Group B were lost to follow-up at 6 months and 1 year visit respectively.

It is observed from the Table that excellent to good response was seen in 85% of cases, while fair response to therapy was observed in 15% of cases at the end of 5 weeks in Group A. In group B excellent to good response was seen in 67.5% of cases and fair response in 32.5% of cases.

At six months and one year follow-up visits excellent to good response was seen in 97% of cases in Group A and 76% in Group B. In the present study, there was no case who showed no response in regression of tumour in both the groups.

Discussion

Failure to cure cancer by radiotherapy is due to the presence of hypoxic cells in the large tumour masses. The various methods to overcome this problem are the use of high LET radiation, hyperbaric oxygen chamber, and chemical radiosensitizers of hypoxic tumour cells. The chemical radiosensitizer Metronidazole is favoured pharmacologically and toxicologically as reported by Goodman and Gillman. It has also a cytocidal action. Mogre, *et al* (1979) studied the role of Metronidazole as a chemical radiosensitizer in human carcinomas.

TABLE II
Objective Response

	Group A			Group B		
	Excellent	Good	Fair	Excellent	Good	Fair
5 weeks	23 (57.5%)	11 (27.5%)	6 (15%)	19 (47.5%)	8 (20%)	13 (32.5%)
3 months	25 (62.5%)	12 (30%)	3 (7.5%)	21 (52.5%)	10 (25%)	9 (22.5%)
6 months	25 (69.5%)	10 (27.7%)	1 (2.8%)	20 (54%)	8 (21.6%)	9 (24.4%)
1 year	25 (73.5%)	8 (23.5%)	1 (3%)	17 (51.5%)	8 (24.7%)	8 (24.7%)

One hundred and twenty patients of difference age groups suffering from various types of cancer receiving radiations were included in the study. Of these 100 cases belonged to stage III cervical malignancy. 60% cases showed complete regrescion of tumour at the end of 5 weeks, and 20% showed partial regression at the end of 5 weeks.

Ayyagari (1979) studied 40 cases of stage II and III cancer cervix receiving radiotherapy, 20 in control group and 20 in Metronidazole group. In their study, complete regression was observed in 50% cases in control group, while it was 66% in Metronidazole group at the end of 5 weeks.

A double blind clinical trial was carried out in 80 patients to evaluate the response of advanced cervical malignancy to radiation following radiosensitization of the hypoxic cells with metronidazole. This study showed excellent response in 57.5% of the cases, good response in 27.5%, of cases and fair in 15% of cases in Group A; while in Group B 47.5% of cases showed excellent response, 20% showed good response and 32.5% of case showed fair response at the end of 5 weeks. These cases were further followed for I year At the end of one year; 73.5% showed excellent, 23.5% showed good and 3% showed fair response in Group A, while 51.5% had excellent, 24.7% had good and 24.7 had fair response in Group B.

This clearly shows that radiosensitizing effect of Metronidazole and its place in the treatment of advanced cervical malignancy.

When the excellent response of the two groups — Metronidazole (A) and control (B) is compared, it may be concluded that Metronidazole group showed complete regression in 10% more cases as against control group at the end of 5 weeks. At the one year follow-up the difference of excellent response in the two groups, 22% in group A more.

Acknowledgement

We wish to thank the Dean of the Govt. Medical College and Hospital, Nagpur for allowing this study. We are also thankful to the Unique Pharmaceuticals Ltd., for supplying Tab. Metrogyl for the trial.

References

1. Ayyagari, S.: (Quoted by Unique group of Phar. Personnel communication) 1979.
2. Goodman, S. and Gilman, A.: The pharmacological Basis of Therapeutics ed. 6, New York 1980, Macmillan Publishing Co., P. 1077.
3. Gray, L. H.: Brit. J. Radiol., 26: 638, 1953.
4. Mogre, K., Bhalavat, R. L. and Pinto, J. M.: Ind. J. Cancer Chemotherapy, I: 3, 1979.