COMBINED CANCER CHEMOTHERAPY AND RADIOTHERAPY IN THE TREATMENT OF HUMAN CANCER*

GEOFFREY FALKSON,‡ M.B., CH.B., M.MED. (INT.), M.D. AND THEUNIS FICHARDT,† M.D., D.SC., M.MED. (RAD.T.), F.F.R. (R.C.S.I.), *Pretoria General Hospital and University of Pretoria*

The most important problem in combining two forms of treatment is to ensure that the combination, which usually involves decreasing the dosage of both forms of treatment, is more effective than maximum tolerated doses of each moiety on its own. The only acceptable proof is the clinical result which is achieved. We will, therefore, attempt to summarize some of the results achieved by combined cancer chemotherapy and radiotherapy.

Combined radiotherapy and chemotherapy give the best results in the treatment of advanced cancer of the stomach, pancreas, ovary, head and neck, and lung, as well as in nephroblastoma, malignant melanoma and malignant mesothelioma. This is quite apart from the very long list of advanced neoplasms such as breast cancer and the reticuloses, where both radiotherapy and chemotherapy are used, often together, in a simple additive fashion. These combination treatments have been developed only within the last few years. Except in the treatment of retinoblastoma, combined radiotherapy and chemotherapy are used almost exclusively for advanced cancer with metastases and never as a substitute for curative surgery or curative radiotherapy.

Since the discovery of the damaging effects of ionizing radiations on cancer cells, attempts have been made to increase the radiation curability of malignant neoplasms by the simultaneous administration of various agents.

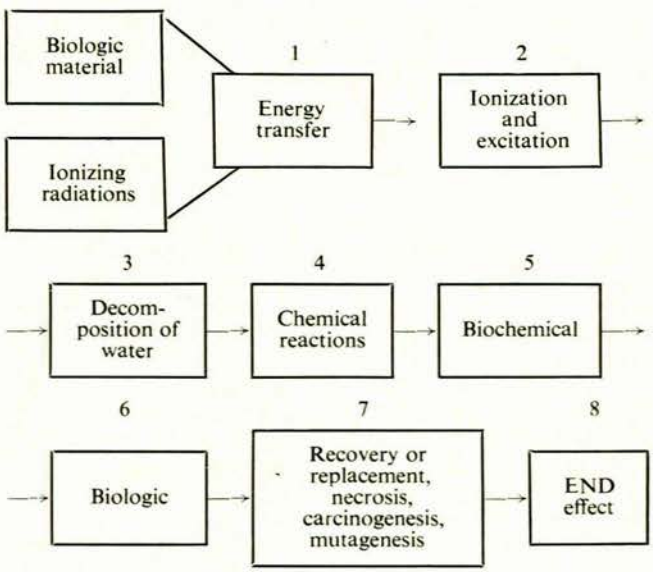
At the present time the emphasis is on therapeutic synergism. For purposes of discussion we can include potentiation, sensitization and augmentation as synonymous with synergism, that is, response greater by combined treatment than could be predicted from doses of the individual agents alone. The problem of modification of the radiation response in human cancer therapy is complex, because we are never concerned with a single response, such as cancerocidal effect, but always with an interrelationship of responses—the total host-tumour response.

Table I illustrates in schematic fashion the sequence of events in radiation response.[1] The synergistic effect of oxygen may act at step 3. In step 4 the presence of oxygen may also augment radiation response. Despite the fact that step 5 is the least clearly defined in the mechanism of radiation response, this is nevertheless the area where most clinical attempts at modification have been tried, for, presumably, this is also the point where anticancer agents act.

Synkavit

The most stimulating studies on the therapeutic modification of radiation response have been those of the Cambridge University research workers under Prof. J. S. Mitchell. Since 1946 they have examined about 170 compounds for use as radiosensitizers.[2] Compound I, the tetra-sodium salt of 2-methyl-1 : 4-naphthohydroquinone diphosphate (Synkavit, Roche), a water-soluble compound of low toxicity administered by intravenous route, appears to be the best chemical radiosensitizer. These authors state that 'mitotic inhibition' is probably not the only factor involved, neither is it the most important factor to be considered.[3]

TABLE I. SEQUENCE OF EVENTS IN RADIATION RESPONSE



Mitchell *et al.*[4-11] have published numerous reports on the radiosensitizing action of Synkavit on animal tumours as well as reports on clinical trials with this agent. Recently, at the First International Symposium on Radiosensitizers and Radioprotective Drugs, held at Milan (1964),[12] Professor Mitchell gave an interesting account of their clinical studies with Synkavit. In a randomized trial of inoperable carcinoma of the bronchus their patients were divided into 4 groups. These groups were: (1) intravenous Synkavit and X-ray therapy—83 cases, (2) oxygen, intravenous Synkavit and X-ray therapy—69 cases, (3) intravenous compound 28 [2,3-dimethyl-1 : 4-naphthaquinol bis-(disodium phosphate)] and X-ray therapy—57 cases, and (4) oxygen and X-ray therapy—60 cases. The best survival curves were seen in the group that received intravenous Synkavit before radiotherapy, and oxygen inhalation before and during the X-ray therapy. Lowest survival curves were seen in the group receiving oxygen and X-ray therapy. Assessment, however, has not yet been completed. Reports by Deely[13] and Konecny,[14] in 1962, have confirmed the clinical response in the treatment of bronchus carcinoma with Synkavit combined with X-ray.

The Cambridge workers have attempted to develop a radioactive drug for treatment of neoplastic disease. Studies on the selective concentration of Synkavit in

*Paper presented at the 45th South African Medical Congress (MASA), Port Elizabeth, June - July 1965.

‡Consultant cancer chemotherapist. In receipt of a grant from the National Cancer Association of South Africa.

†Professor and Director, Department of Radiotherapy.

tumour cells suggested the possibility that the incorporation of tritium into the Synkavit molecule might have promising therapeutic possibilities.[15-18] Marrian *et al.*[19] devised a method of tritiation which has yielded more reliable preparations. One of these more reliable agents, TRA 72, has produced useful clinical palliation in 12 out of 46 seriously ill patients.

A tritiated Synkavit of even higher specific activity has been prepared, namely TRA 119,[19] and in the British Empire Campaign's Annual Report in 1962, Professor Mitchell reported on the use of this agent in 33 patients with advanced neoplastic disease.[20,21]

It was found that in most tumour cells compound TRA 119 is present in the cytoplasm and perhaps within the substance of the nuclear membrane; in some cells there was a concentration around the nucleoli, sometimes to a high degree.[22] It is important that autoradiographic studies showed no uptake by sternal marrow of TRA 119, and no appreciable change in the blood picture. However, a few rare unidentified cells were found in the bone marrow of some cases.[23]

Colchicine

Colchicine, combined with radiotherapy in the treatment of malignant disease, has been used by various authors.[22-33] The lack of adequate controls complicates the evaluation of results. There appears to be no conclusive evidence that colchicine is of any practical value as a radiosensitizer.

A less toxic derivative of colchicine, N-deacetylthiocolchicine, has also been used in combination treatment.[34] Tarnowski and co-workers (1958)[35] found no significant increase in tumour regression in experimental animals with this combined method. Italian workers reported on 100 cases of radio-resistant human tumours treated with 2,000 - 3,000 rads plus various mitotic inhibitors (30 cases with colchicine, 30 cases with colchicine derivatives, 20 cases with podophyllin derivatives and 20 cases with ethylic urethan). They claim some regressions without important radiation damage in patients treated with colchicine and X-ray therapy.[36]

Alkylating Agents

The effects of alkylating agents resemble those of ionizing radiations in many respects. However, there are definite differences in both the chemical mechanisms of action and the cytological effects of radiation and alkylating agents, and therefore Bane *et al.* (1957)[37] feel that the possibility exists that combinations of ionizing radiation with alkylating agents may produce not only additive but also synergistic effects by interfering with cell division in more than one way.

Some authors report remissions in lung cancer which they ascribe to the combination of nitrogen mustard and X-ray therapy.[38-41] Many authors, however, find that clinical results are not superior to those obtained with radiation alone.[42-46] Regional intra-arterial application of nitrogen mustard and simultaneous radiation give good tumour regression in patients with carcinoma of the oral cavity.[47] Beneficial effect in spinal cord tumours from combined therapy are higher than from radiotherapy alone.[48]

When a combination of TEM and radiotherapy is used for the treatment of retinoblastoma, the *cure rate* has been greatly increased over that with radiotherapy alone.[49-55] The results, however, of a combination of TEM and X-ray therapy for lung cancer have shown only more tumour destruction.[42]

Chlorambucil in combination with radiotherapy has given some encouraging results in ovarian[51,56] and endometrial carcinoma.[51]

ThioTEPA in combination with radiotherapy has also given good results in ovarian carcinoma.[57,58] Results in bronchogenic carcinoma have not been improved.[51]

Chevalier *et al.*[59] discuss experimental and clinical findings on the combination of radiation and cyclophosphamide. They conducted clinical trials on bronchial tumours, and although they observed a summation of effect, there was no therapeutic difference. In the treatment of childhood neuroblastoma with cyclophosphamide plus radiotherapy, Kontras and Newton[60] report better response in all of their 4 patients treated in this way, than in 9 other patients who did not receive combined treatment. Although there are several reports in the literature on the use of cyclophosphamide in combination with X-ray therapy,[61-64] no evidence is presented that this agent is a radiopotentiator or radiosensitizer. We have found that cyclophosphamide does not act as a radiopotentiator or radiosensitizer.[65,66] When a localized area of bone or skin metastases is having radiotherapy for symptomatic relief, we have found it useful to combine the radiotherapy with cyclophosphamide therapy if the patient is suffering from generalized malignancy, e.g. breast cancer with metastases, but then each agent acts on its own; there is no potentiation.

AB-132, in combination with radiotherapy, reduces the size of the tumour in bronchogenic carcinoma in 4 out of 5 patients,[67] and in the treatment of 15 patients with carcinoma of head and neck better results were obtained than with either form of treatment alone.[68] At the present time alkylating agents such as cyclophosphamide and chlorambucil plus radiotherapy can be considered the treatment of choice in advanced ovarian cancer.

Antibiotics

Farber[69,70] maintains that most patients with Wilm's tumour are now treated with consistent success by the combination of Actinomycin D and radiotherapy. Several clinical reports dealing with the radiopotentiating effect of Actinomycin D have appeared by D'Angio and co-workers,[70-75] Tan *et al.*,[76] Altman,[77] Kirkpatrick *et al.*,[78-80] and Clark *et al.*[81,82] Griem and Ranniger[83] reported on their preliminary clinical findings at the First International Symposium on Radiosensitizers and Radioprotective Drugs at Milan. Some unexpected responses are seen in patients with multiple myeloma. The skin and mucous membrane of some patients show an enhancement and acceleration of the normal reactions to X-ray therapy after combined treatment.[84] Actinomycin D may reactivate latent radiation responses within skin returned to normal appearance after previous radiotherapy.

Other antibiotics that give improved clinical results when used in combination with radiation are: Chromomycin,[85] the Russian antibiotic Aurantin,[86] and Mitomycin C.[87] We have not observed radiopotentiation with Chromomycin.[88]

Miscellaneous Compounds

Many agents in combination with X-ray therapy in the treatment of human cancer have been used with equivocal results. Sometimes the agents are used because of some vague preconceived hypothesis as to the possible mechanism of modification of radiation response; often they are used on a purely empirical basis. Schwartz *et al.*,[89] at the University of Minnesota, investigated the possibility of porphyrins as modifiers of the effects of X-ray therapy.

Loken[90] states that several considerations made it conceivable that the haeme enzyme metabolism of tumours might have a modifying effect on the action of ionizing radiation. The published review shows that one-third of the patients had a greater response. Japanese workers report better clinical response in 46 patients with various types of malignant disease, treated with X-rays combined with mercury haematoporphyrin,[85] and Ogata[91] reports response in 3 cases of lung cancer treated with ^{60}Co + mercury haematoporphyrin. Mack *et al.*[92] report good response in some patients with cervical cancer treated with this combination.

At the First International Symposium on Radiosensitizers and Radioprotective Drugs held at Milan, several papers were read by Italian workers on the use of sodium cyclohexanol succinate ('Radioplex') in combination with radiotherapy. Lamberts,[93] however, failed to show any sensitizing or protective effects with this agent.

Baclesse and Delaplace,[94] at the Foundation Curie, in Paris, used intratumoural cesium eosinate as radiosensitizer and they reported a favourable response in 30 out of 65 patients with various malignancies.[94,95] These workers also used another substance, Glyoxal (a polycarbonyl compound) intravenously; this they found rather toxic. They also found great individual variation in response to radiosensitizing substances, which could not be correlated with histologic type or with the extent of the tumour.[95]

Hydrogen peroxide has been used in combination with X-ray therapy as a source of oxygen in the treatment of carcinoma of the head and neck by workers at the Baylor University, Texas.[96] H_2O_2 used as an ointment permitted a reduction of radiation dose of 1,000 - 1,500r in the treatment of skin cancer in 106 cases.[97] Workers at the Roswell Park Memorial Institute failed to show any enhancement of radiation by the use of H_2O_2 in a group of animal experiments.[98]

Ro4-6467

Alpha-(2-methylhydrazino)-p-toluamide hydrochloride, (Natulan, Ro4-6467) is a synthetic derivative of methylhydrazine which has proved to be of value in the treatment of Hodgkin's disease.[99-101]

Falkson and Jacobs[102] published the first report on this agent recording its clinical value as a radiosensitizer. We now find this agent to be of value as a radiosensitizer in patients with malignant mesothelioma and malignant melanoma, and are continuing these investigations. One of our patients was a man with radio-resistant cancer of the penis who had developed advanced ulcerating inguinal metastases. These lesions are now under complete control following Natulan treatment with concomitant radiotherapy. Brulé *et al.*[103] have reported that Natulan is of value in the treatment of bronchial cancer. Since the beginning of 1964 we have been conducting clinical trials in an attempt to determine the value of this agent combined with radiotherapy in the management of cancer of the bronchus. So far encouraging results have been obtained.

Fluorinated Pyrimidines

Since the original paper by Heidelberger and coworkers in 1958[104] on the screening of fluorinated pyrimidines, and their demonstration that the combination of FU and X-ray therapy was superior to either agent alone against sarcoma 180 and adenocarcinoma 755, various scientists have done work on the combined effects of halogenated pyrimidines and ionizing radiation. Vermund *et al.*[105] confirm the findings of Heidelberger and his coworkers. They found that combined therapy in the treatment of spontaneous mammary carcinomas in mice was better than when either agent was used on its own. Bagshaw[106] demonstrated the same effect on cells grown *in vitro*. B. E. Hall, who first reported (1959) at a fluorouracil symposium in Madison on the excellent antitumour effects of combined X-ray and 5-fluorouracil therapy on primary bronchogenic carcinomas, substantiated the observations of Heidelberger *et al.* and Vermund *et al.* His enthusiastic reports have stimulated many others to carry out clinical trials on combined therapy with these two agents.

In February 1960 Falkson and Snyman[66] reported their experience with the first two patients to receive this, then undescribed, form of treatment, namely 5FU plus radiotherapy in the treatment of cancer of the stomach. Both these patients showed a good objective response. In 1961 Fichardt and Jacobs recorded their experience in the treatment of 57 cases of advanced cancer of the stomach treated with combined 5FU and telecobalt therapy, with encouraging results. Three subsequent publications by our group[107-109] contain the largest series of cases of stomach cancer treated by this method. The skin changes occurring as a result of the combined 5FU and radiotherapy were described by Falkson and Schulz in 1962.[110]

Table II shows the results obtained by combining adequate doses of 5FU with radiotherapy.

TABLE II. STOMACH CANCER: OBJECTIVE REMISSION RATE

Author	*5FU alone*	*5FU + irradiation*
Hall and Good[116] (San Francisco)	1/2	4/6
Korst and Allaire[117] (Ann Arbor)	1/4	2/3
Langdon *et al.*[120] (Univ. California)		3/4
Sklaroff[58] (Philadelphia)		5/10
Falkson *et al.*[107-110] (Pretoria)	3/18	66/121

At the 56th Annual Meeting of the American Association for Cancer Research, held in April 1965, Moertel, Reitemeier, Childs, Holbrook, and Colby,[111] of the Mayo Clinic at Rochester, in a double-blind comparison of supervoltage radiation therapy alone and combined with 5-fluorouracil, confirmed our observations that combined therapy of gastric carcinoma resulted in a significant prolongation of survival time. (See also Table III.)

Since the growth of normal squamous (or columnar) epithelium was seriously impaired by the administration of FU, it seemed logical to assume that rapidly growing, anaplastic carcinomas of squamous cell origin might

absorb enough FU to interfere with the metabolism of individual tumour cells, even though not in a sufficiently high concentration to produce tumour cell death, thus making them more susceptible to the cancerocidal effects of ionizing radiation. In initial studies to test this hypothesis, Hall *et al.*[112-114] and Foye *et al.*[115] treated patients

TABLE III. REPORTS OF SUPERIOR EFFECT OF 5FU COMBINED WITH RADIOTHERAPY IN TREATMENT OF HUMAN NEOPLASMS

Author	*Tumour*		
	Bronchus	*Head and neck*	*Bladder*
Hall *et al.* (1959, 1960, 1962)	+	+	
Foye *et al.* (1960)	+	+	
Korst *et al.* (1961)	+		
Langdon *et al.* (1963) ..	O		
Sklaroff (1962)	O		
Crews (1961)	O		
Frank *et al.* (1961, 1962) ..	+		
Griffing *et al.* (1961)	+		
Woodruff *et al.* (1962) ..			+
Brady *et al.* (1963)			+
Hosley *et al.* (1962)	O		
Schlosser (1962)	+	+	+
Helsper & Sharp (1962) ..	+		
Bagshaw (1961, 1963) ..	+	+	
Howe *et al.* (1964)		+	
Wisconsin group (1964) ..	+	+	
T. C. Hall (1964) ..	Different dosage schedule O		

with inoperable squamous cell carcinoma of the lung and of the head and neck, simultaneously with FU and orthovoltage irradiation to estimated tumour doses of no more than 2,000r. Unusually rapid rates of tumour regression were observed in almost all cases leading to the postulation that there was either an additive effect when the two modes of therapy were used simultaneously or one mode of therapy potentiated the antitumour effect of the other. Subsequently it was learned that more effective palliation often could be obtained by combined therapy in patients with tumours susceptible to FU alone, when there was a specific target in need of radiation.

Hall and Good[116] report their experience in 223 patients with advanced cancer of whom 72 were treated with FU alone and 151 with combined therapy. The authors found radiotherapy combined with FU useful in the treatment of certain metastatic lesions in the lungs and for the relief of pain and/or obstructive symptoms caused by recurrent, inoperable growths in which full doses of radiotherapy could not be given because of the previous administration of X-ray therapy. They observed remissions with the combined method of treatment particularly in recurrent, inoperable, previously irradiated carcinomas of the head and neck. Unusually rapid regression of the primary focus may be observed when the combined method of treatment is used in carcinomas of the lung and oesophagus, but prolonged remissions are seldom obtained because of the high and relatively rapid rate of local recurrence, especially with carcinoma of the oesophagus.

Korst *et al.*,[117,118] from Ann Arbor, report on a series of 106 patients with various malignancies. In 53 patients FU was administered alone and in 32 FU was administered in combination with X-ray therapy; in 21 the results could not be evaluated. They obtained encouraging palliative results with combined FU and X-ray therapy in gastro-intestinal and pulmonary neoplasms.

A limited randomized study in the treatment of inoperable bronchogenic carcinoma, by Ansfield and co-workers in Wisconsin,[119] suggested that the combination of FU plus radiotherapy resulted in an increase in the average survival time when compared with that attained with radiation alone. Of the 13 patients receiving FU combined with supervoltage therapy, the average survival time was 15·7 months; of 13 receiving supervoltage alone, the average survival time was 6·2 months. All survivals were calculated from the onset of therapy. Advanced head and neck carcinomas appeared to respond better to combined therapy than to radiotherapy alone in a non-randomized group.

Langdon *et al.*,[120] from the University of California, reported on 99 cases of solid tumours treated with combined radiotherapy and FU, or Actinomycin D, or Mitomycin C or Leukoran. They observed no significant difference in response in their 47 cases of bronchogenic carcinoma. Seven cases of gastric adenocarcinoma are included in their series. In 3 of the 4 who reached the significant level of dosage combination 'good' or 'excellent' results were achieved. They also published a report on side-effects encountered with this method of treatment,[121] and concluded that gastro-intestinal toxicity and haematopoietic responses were most important and of the highest incidence.

Sklaroff,[58] from Philadelphia, reported his experience with chemotherapy and telecobalt therapy at the International Cancer Congress in Moscow in 1962. Of the 30 patients with carcinoma of the colon, 25 received combined treatment; and of these an objective response lasting 3 months occurred in 9 patients. Seven patients showed an objective response lasting 6 months or more. Of the 30 patients with advanced inoperable lung carcinoma, 18 received combined therapy; 10 showed improvement lasting 2 - 10 months.

Friedman,[122,123] from New York, reports on 40 patients, most with multiple lesions, who received supervoltage therapy (± half the usual tumour dose or, if the tumours were very large, 5,000r) plus intravenous FU. He concludes that: 'Some cases demonstrated that radiation unquestionably enhanced chemotherapy; some cases showed that chemotherapy probably enhanced radiation.'

Crews,[124] from Los Angeles, reports treating 33 patients with advanced solid malignancies. He found that the effect on the gastro-intestinal tract was greater than for radiotherapy alone. 'Good' palliation was noted in one-third of the patients, 'poor' palliation in another third, and 'no effect' in one-third.

Frank and co-workers,[125-127] from the Walter Reed Hospital, Washington DC, state that they administered FU concomitant to radiotherapy of the tumour in 26 patients with a variety of malignancies, mostly lung cancer. In 10 of the 26 patients there was reduction of toxicity, but retention of antitumour activity.

Griffing *et al.*,[128] from Baltimore, reported on 25 patients treated with FU, before the daily dose of radiotherapy. Woodruff *et al.*,[129] at the Roswell Park Memorial Hospital, treated 17 patients with infiltrating transitional cell car-

cinoma of the urinary bladder; 14 received FU and concomitant X-ray therapy, 3 received FU and non-concomitant X-ray therapy. Regression was observed in 6 patients. Brennan *et al.*[130] state that it is possible that radiation may interfere with the response of bladder carcinoma to FU.

Brady and Gislason,[131] of the Hahnemann Medical College, Philadelphia, report that treatment with FU just before supervoltage therapy of 49 patients with bladder carcinoma, significantly increased unfavourable reactions in 5 of the patients.

Hosley *et al.*,[132] at Roswell Park Memorial Hospital, did a controlled pilot study of combination radiation-drug therapy in bronchogenic carcinoma. The median survival time in this group was found to be the same for the treatment group and the control group.

Schlosser,[51] from the Department of Radiotherapy, Tulane University, New Orleans, after 3½ years of experience with various chemotherapeutics in 394 patients, found that the combination of FU and radiotherapy appears to offer the broadest spectrum of effectiveness of all the agents they have tested so far. A good response was seen in carcinoma of the bladder. The FU combination with radiotherapy also appears to offer some promise in bronchogenic carcinomas.

Von Essen *et al.*,[133,134] of the Yale University School of Medicine, studied the effects of FU and X-ray therapy, separately and in combination, upon multiple metastatic tumours within individual patients. Fourteen patients satisfied their criteria for a controlled study. In 4 the effects of irradiation alone were greater than the combination, in 4 the effects were equal, and in 6 the effects of irradiation were less than those of combination therapy. These workers observed the same type of enhanced reaction in previously irradiated skin that we had reported in 1962.[110] These workers felt that their study failed to demonstrate a significant alteration in the tumour response by the addition of FU to X-ray therapy.[134] They have also used IUDR, and reported on 9 patients[135] that there was an increased effect over X-ray therapy alone.

Sharp and Benefiel,[136] from Pasadena, California, reported on 13 cases of colon-rectum carcinoma of whom 7 received FU and concomitant telecobalt therapy.

Several patients showed marked synergistic effects without apparent increase of toxic effects. Helsper and Sharp also treated 8 cases of inoperable carcinoma of the bronchus with combination of FU and telecobalt therapy;[137] 5 controls received telecobalt therapy alone.

The length of remission in those patients treated with combination therapy and weekly maintenance dosage of FU, according to these workers, was approximately 3 times that of patients treated with telecobalt therapy alone. It would appear that the average survival statistics may also be greatly enhanced for those treated with combination therapy. They felt that there seemed to be a definite synergistic effect of telecobalt therapy and FU on bronchogenic carcinoma. The patients treated in this series received not only the maximum tumour dose of radiotherapy, but also a toxic dose of FU. The synchronization seems to result in an increased radiosensitivity.[137]

Bagshaw,[106,138] of the Stanford University, California, treated 15 patients with a variety of malignancies (mostly bronchus or head and neck) with FU combined with radiotherapy. In 7 of the patients tumours regressed more rapidly than was expected.

Howe, Fletcher and co-workers,[37] from the Texas University, Houston, report doing a double-blind study on 21 patients with advanced squamous cell carcinoma of the pharynx. They conclude that the combination appeared to increase the rate of regression of the primary lesions, but did not increase either permanency of the control of the primary or the patient's survival.

Field,[139] from the Institute for Cancer and Leukemia Research, Los Angeles, reports on experience gained over 2½ years in 139 patients of whom 7 received combined X-ray therapy and FU for lung carcinoma. Three of the 7 patients had remissions for longer than 6 months.

Hall,[140] from Boston, reported on a controlled trial by the Eastern Solid Tumour Chemotherapy Corporation at the First International Symposium on Radiosensitizers and Radioprotective Drugs. He found no evidence of additive or synergistic effects for both FU and Actinomycin D in this study, but he used only very small doses of 5FU and radical radiotherapy.

REFERENCES

1. Andrews, J. R. and Sneider, S. E. (1959): Amer. J. Roentgenol., **81**, 485.
2. Mitchell, J. S. (1960): *Studies in Radiotherapeutics*. Oxford: Blackwell Scientific Publications.
3. Mitchell, J. S. and Simon-Reuss, I. (1952): Brit. J. Cancer, **6**, 305.
4. Mitchell, J. S. (1948): *Ibid.*, **2**, 251.
5. *Idem* (1949): Annual Report of the British Empire Cancer Campaign, **27**, 214.
6. *Idem* (1950): *Ibid.*, **28**, 213.
7. *Idem* (1953): Brit. J. Cancer, **7**, 313.
8. *Idem* (1954): Acta radiol. (Stockh.), suppl. 116, 431.
9. *Idem* (1954): Annual Report of the British Empire Cancer Campaign, **32**, 280.
10. *Idem* (1955): *Radiobiological Symposium*, p. 170. London: Academic Press.
11. Mitchell, J. S., Simon-Reuss, I. and King, E. A. (1960): Acta Un. int. Cancr., **16**, 1201.
12. Mitchell, J. S. (1964): 1st International Symposium on Radiosensitizers and Radioprotective Drugs, Milan.
13. Deely, T. J. (1962): Brit. J. Cancer, **16**, 387.
14. Konecny, M. (1962): Cs. Rentgenol., **16**, 50.
15. Horwitz, H., Gregg, C. McC., Marrian, D. H., Marshall, B. and Mitchell, J. S. (1959): Acta radiol. (Stockh.), suppl. 188, 112.
16. Simon-Reuss, I. (1961): *Ibid.*, **56**, 49.
17. Andrews, K. J. M., Bultitude, F., Evans, E. A., Gronow, M., Lambert, R. W. and Marrian, D. H. (1962): J. Chem. Soc., September, 3440.
18. Silver, I. A., Cater, D. B., Marrian, D. H. and Marshall, B. (1962): Acta radiol. (Stockh.), **58**, 281.
19. Marrian, D. H., Marshall, B., Mitchell, J. S. and Simon-Reuss, I. (1962): *Tritium in the Physical and Biological Sciences*. Vienna: International Atomic Energy Agency.
20. Mitchell, J. S. (1962): Annual Report of the British Empire Cancer Campaign, **40**, 16.
21. *Idem* (1963): Proc. Roy. Soc. Med., **56**, 651.
22. Mitchell, J. S., King, E. A., Marrian, D. H. and Chipperfield, B. (1963): Acta radiol. (Stockh.), **1**, 321.
23. Mitchell, J. S. (1964): Personal communication.
24. Huant, E. (1944): Gaz. Hôp. (Paris), **117**, 55.
25. *Idem* (1944): *Ibid.*, **117**, 230.
26. Girgis, A., Martin, J. F., Orsoni, D. and Ponthus, P. (1946): J. Radiol. Électrol., **27**, 244.
27. Griem, M. L., Malkinson, F. D. and Morse, P. H. (1961): Radiology, **77**, 486.
28. Mallet, L. and Le Camus, H. (1944): Presse méd., **52**, 230.
29. Constantin, R. (1964): J. Radiol. Électrol., **27**, 466.
30. Keibl, E. and Loetsch, A. (1950): Schweiz. med. Wschr., **30**, 228.
31. Reviglio, J. M. (1948): Radiol clin. (Basel), **17**, 149.
32. Cohen, S. and Johnson, J. R. (1960): Dis. Chest, **38**, 30.
33. Levine, M. (1951): Ann. N.Y. Acad. Sci., **51**, 1365.
34. Huguenin, R., Truhuat, R. and Saracino, R. (1955): Bull. Ass. franc. Cancer, **42**, 308.
35. Tarnowski, G. S., Bane, H. N., Conrad, J., Nickson, J. J., Stock, C. C. and Sugiura, K. (1958): Cancer Res., **18**, 225.
36. Bonomini, B. and Fiorentino, M. (1964): 1st International Symposium on Radiosensitizers and Radioprotective Drugs, Milan.
37. Bane, H. N., Conrad, J. T. and Tarnowski, G. S. (1957): Cancer Res., **17**, 551.
38. Lings, H. (1950): Strahlentherapie, **81**, 379.
39. Roswit, B. and Kaplan, G. (1951): Radiology, **57**, 384.
40. Watson, T. A. (1956): Amer. J. Roentgenol., **75**, 525.
41. Krabbenhoft, K. L. and Leucutia, T. (1958): *Ibid.*, **79**, 491.
42. Lochman, D. J. and Morris, R. S. (1956): Radiology, **66**, 842.
43. Hughes, F. A. jnr., Pate, J. W. and Campbell, R. E. (1960): J. Thorac. Cardiovasc. Surg., **39**, 409.

44. Krant, M. J. and Chalmers, T. C. (1962): Proc. Amer. Assoc. Cancer Res., **3**, 335.
45. Alexander, L. L., Causing, J., Schwinger, H. N. and Li, M. C. (1962): Amer. J. Roentgenol., **87**, 375.
46. Chalmers, T. C. (1962): Cancer Chemother. Rep., **16**, 463.
47. Lebrun, J., Henry, J., Simon, S. and Smets, W. (1961): Bull. Ass. franc. Cancer, **47**, 597.
48. Williams, H. M., Diamond, H. D. and Craver, L. F. (1958): Cancer (Philad.), **11**, 76.
49. Reese, A. B., Hyman, G. A., Merriam, G. R., Forrest, A. W. and Kligerman, M. M. (1955): Arch. Ophthal., **53**, 505.
50. Reese, A. B., Hyman, G. A., Tapley, N. du V. and Forrest, A. W. (1958): *Ibid.*, **60**, 897.
51. Schlosser, J. V. (1962): Bull. Tulane Med. Fac., **21**, 65.
52. Tapley, N. du V. *in* Kallman, R. F., ed. (1961): *Research in Radiotherapy, p.* **199**. Washington: National Academy of Science.
53. Krementz, E. T., Schlosser, J. V. and Rumage, J. P. (1962): Cancer Chemother. Rep., **16**, 571.
54. Harger, R. W. (1960): J. Indiana Med. Assoc., **53**, 662.
55. Hyman, G. A., Ellsworth, R. M. and Reese, A. B. (1964): Acta Un. int. Cancr., **20**, 407.
56. Miller, S. P. and Brenner, S. M. (1962): Cancer Chemother. Rep., **16**, 455.
57. Howe, C. D., Fletcher, G. H., Samuels, M. L. and Smit, H. D. (1964): Acta Un. Int. Cancr., **20**, 400.

57a. Kottmeier, H. L. (1962): *Modern Trends in the Treatment of Patients with Semi-malignant and Malignant Ovarian Tumours,* p. 285. Chicago: Year Book Medical Publishers.

58. Sklaroff, D. M. (1964): Acta Un. int. Cancr., **20**, 404.
59. Chevalier, A., Herdly, J., Manuel, S. and Chateau, D. (1964): 1st International Symposium on Radiosensitizers and Radioprotective Drugs, Milan.
60. Kontras, S. B. and Newton, W. A. (1961): Cancer Chemother. Rep., **12**, 39.
61. Spechter, H. J. (1961): Krebsforschung und Krebsbekämpfung, **4**, 86.
62. *Idem* (1961): Med. Hyg., **19**, 436.
63. Ramioul, H. and Zutterman, R. (1961): Acta clin. belg., **16**, 271.
64. West, W. O. (1962): Arch. Intern. Med., **109**, 469.
65. Falkson, G. and Snyman, H. W. (1964): Acta Un. int. Cancr., **20**, 439.
66. Snyman, H. W. and Falkson, G. (1960): Geneeskunde, **2**, 40.
67. Ross, C. A., Velasco, H. A., Sokall, J. E., Ambrus, J. L., Stutzman, L., Webster, J. and Bardos, T. J. (1962): Proc. Amer. Assoc. Cancer Res., **3**, 355.
68. Watne, A. L., Bozzini, M. A., Mukhtar, F. A., Marchetta, F. C. and Moore, G. E. (1962): Cancer Chemother. Rep., **25**, 101.
69. Farber, S. (1962): *Ibid.*, **16**, 603.
70. *Idem* (1961): *Ibid.*, **13**, 159.
71. D'Angio, G. J., Brown, B. L., Maddock, C. L. and Sunda, V. (1961): Proc. Amer. Assoc. Cancer Res., **2**, 217.
72. D'Angio, G. J., Farber, S. and Maddock, C. L. (1959): Radiology, **73**, 175.
73. Farber, S., D'Angio, G. J., Evans, A. and Mitus, S. (1960): Ann. N.Y. Acad. Sci., **89**, 421.
74. D'Angio, G. J. (1962): Amer. J. Roentgenol., **87**, 106.
75. *Idem* (1963): Laval méd., **34**, 137.
76. Tan, C. T. C., Dargeon, H. W. and Burghenal, J. H. (1959): Pediatrics, **24**, 544.
77. Altman, D. H. (1961): Amer. J. Roentgenol., **86**, 673.
78. Kirkpatrick, G. P. (1961): Proc. Inst. Med. Chic., **23**, 300.
79. Liebner, E. J., Kirkpatrick, G. P. and Rosenthal, I. M. (1962): Illinois Med. J., **121**, 531.
80. Liebner, E. J. (1962): Amer. J. Roentgenol., **87**, 94.
81. Clark, A. C. L. (1962): Med. J. Aust., **1**, 512.
82. Colebatch, J. H., Howard, R., Williams, A. L., Kurrle, G. R. and Clark, A. C. L. (1964): Acta Un. int. Cancr., **20**, 491.
83. Griem, M. L. and Ranniger, K. (1964): 1st International Symposium on Radiosensitizers and Radioprotective Drugs, Milan.
84. Maddock, C. L., Brown, B., D'Angio, G. J. and Tedeschi, C. (1960): Fed. Proc., **19**, 352.
85. Tamura, K., Kishigami, K., Tottori, K. and Yoshikawa, M. (1961): Nippon acta radiologica, **21**, 441.
86. Maevski, M. M. (1961): Vop. Onkol., **7**, 123.
87. Fiorentino, M. and Pratese, P. (1961): Radiol. med. (Torino), **47**, 867.
88. Falkson, G., Falkson, H. C. and Sandison, A. G. (1964): Med. Proc., **10**, 264.
89. Schwartz, S., Absolon, K. and Vermund, H. (1955): Univ. Minn. Med. Bull., **27**, 7.
90. Loken, M. K. (1957): Radiology, **69**, 201.
91. Ogata, Y. (1961): Nippon acta radiologica, **21**, 83.
92. Mack, H. P., Diehl, W. K., Peck, G. C. and Figge, F. H. J. (1957): Cancer (Philad.), **10**, 529.
93. Lamberts, H. B. (1964): 1st International Symposium on Radiosensitizers and Radioprotective Drugs, Milan.
94. Baclesse, F. and Delaplace, R. (1960): Antibiot. et Chemother. (Basel), **8**, 374.
95. Baclesse, F. (1960): Acta Un. int. Cancr., **16**, 1261.
96. Mallams, J. T., Finney, J. W. and Balla, G. A. (1962): Sth. Med. J. (Bgham, Ala.), **55**, 230.
97. Gartmenn, H. and Hoefs, W. (1961): Arch. klin. exp. Derm., **213**, 136.
98. Ausman, R., Hartman, L., Meszaros, L. and Strauss, G. (1963): Proc. Amer. Assoc. Cancer Res., **4**, 3.
99. Mathé, G., Schweisguth, O., Schneider, M., Amiel, J. L., Berumen, L., Brule, G., Cattan, A. and Schwarzenberg, L. (1963): Lancet, **2**, 1077.
100. Martz, G., D'Alessandri, A., Keel, H. J. and Bollag, W. (1963): Cancer Chemother. Rep., **33**, 5.
101. Falkson, G., De Villiers, P C and Falkson, H. C. (1965): In the press.
102. Falkson, G. and Jacobs, E. L. (1964): Med. Proc., **10**, 452.
103. Brulé, G., Schlumberger, J. R. and Griscelli, C. (1965): Cancer Chemother. Rep., **44**, 31.
104. Heidelberger, C., Griesbach, L., Montag, B. J., Mooren, D., Cruz, O., Schnitzer, R. J. and Grunberg, E. (1958): Cancer Res., **18**, 305.
105. Vermund, H., Hodgett, J. and Ansfield, E. J. (1961): Amer. J. Roentgenol., **85**, 559.
106. Bagshaw, M. A. (1961): *Ibid.*, **85**, 822.
107. Falkson, G., Sandison, A. G., Jacobs, E. L. and Fichardt, T. (1963): S. Afr. Med. J., **37**, 712.
108. Falkson, G. (1964): 'Fluorinated pirimidines as potentiators of ionizing radiations in the treatment of stomach cancer in man', M.D. thesis, University of Pretoria.
109. *Idem* (1965): S. Afr. J. Radiol., **3**, 14.
110. Falkson, G. and Schulz, E. J. (1962): Brit. J. Derm., **74**, 229.
111. Moertel, C. G., Reitemeier, R. J., Childs, D. S., Holbrook, M. A. and Colby, M. Y. (1965): Proc. Amer. Assoc. Cancer Res., **6**, 46.
112. Hall, B. E., Foye, L. V. jnr., Roth, M., Willett, F. M., Hales, D. R., Ward, J. H. jnr., Butler, H. T. and Godfrey, M. H. (1960): Lancet, **1**, 115.
113. Hall, B. E., Willett, F. M., Foye, L. F., Good, J. W., Ward, J. H. jnr. (1960): Proc. Amer. Assoc. Cancer Res., **1**, 116.
114. Hall, B. E. and Good, J. W. (1960): Trans. Amer. Clin. Climat. Assoc., **72**, 119.
115. Foye, L. V., Willett, F. M., Hall, B. E. and Roth, M. (1960): Calif. Med., **93**, 288.
116. Hall, B. E. and Good, J. W. (1962): Cancer Chemother. Rep., **16**, 369.
117. Korst, D. R. and Allaire, F. J. (1961): Proc. Amer. Assoc. Cancer Res., **2**, 241.
118. Allaire, F. J., Thieme, E. T. and Korst, D. R. (1961): Cancer Chemother. Rep., **14**, 59.
119. Gollin, F. F., Ansfield, F. J. and Vermund, H. (1964): Geriatrics, **19**, 365.
120. Langdon, E. A., Ottoman, R. E., Rochlin, D. B. and Smart, C. R. (1963): Radiology, **81**, 1008.
121. Ottoman, R. E., Langdon, E. A., Rochlin, D. B. and Smart, C. R. (1963): *Ibid.*, **81**, 1014.
122. Friedman, M. (1961): Proc. Amer. Assoc. Cancer Res., **2**, 226.
123. *Idem* (1963): J. Bone Jt Surg., **45A**, 211.
124. Crews, Q. E. jnr. (1961): Cancer Chemother. Rep., **14**, 45.
125. Frank, W., Brennan, J. T. and LoPresti, J. M. (1961): *Ibid.*, **11**, 145.
126. Frank, W., Newcomer, K. L., Cirksena, W. J., Bauer, A. J. and Blom, J. (1962): *Ibid.*, **22**, 55.
127. Frank, W., Brennan, J. T., Newcomer, K. L. and Cirksena, W. J. (1962): Med. Ann. D.C., **31**, 12.
128. Griffing, J., Sayler, C., Vann, P. and Sensenbrenner, L. (1961): Cancer Chemother. Rep., **12**, 63.
129. Woodruff, M. W., Murphy, W. T. and Hodson, J. M. (1962): *Ibid.*, **21**, 123.
130. Vaitkevicius, V. K., Brennan, M. J., Beckett, V. L., Kelly, J. E. and Talley, R. W. (1961): Cancer (Philad.), **14**, 131.
131. Brady, L. W. and Gislason, G. J. (1963): Amer. J. Roentgenol., **89**, 150.
132. Hosley, H., Marangoudakis, S., Ross, C. A., Murphy, W. T. and Holland, J. F. (1962): Cancer Chemother. Rep., **16**, 467.
133. Von Essen, C. F., Calabresi, P., Kligerman, M. M. and Finch, S. C. (1960): Proc. Amer. Assoc. Cancer Res., **1**, 159.
134. Von Essen, C. F., Kligerman, M. M. and Calabresi, P. (1963): Radiology, **81**, 1018.
135. Kligerman, M. M. (1961): Proceedings of the Conference on Research and Radiotherapy in Cancer, p. 147.
136. Sharp, G. S. and Benefiel, W. W. (1962): Cancer Chemother. Rep., **20**, 97.
137. Helsper, J. T. and Sharp, G. S. (1962): *Ibid.*, **20**, 103.
138. Bagshaw, M. A. (1963): Laval méd., **34**, 124.
139. Field, J. B. (1962): Clin. Res., **10**, 120.
140. Hall, T. C. (1964): 1st International Symposium on Radiosensitizers and Radioprotective Drugs, Milan.