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MANTLE TREATMENT OF HODGKIN'S DISEASE

Preliminary report of side effects and early results

by

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The rationality of irradiation not only of involved but also of adjacent, clinically apparently uninvolved lymph node groups in patients with local Hodgkin's disease, has been stressed by PETERS (1950, 1966), PETERS & MIDDLEMISS (1958), KAPLAN (1962, 1966), SALZMAN et coll. (1964), JELLIFFE (1965) and NOBLER (1968), and others.

In recent years, the mantle technique has been widely used in the treatment of supradiaphragmatic disease. The recommended absorbed dose in the target for this technique is generally about 4 000 rad in 4 weeks. (For further comments on the modification of technique and dose level, reference is made to SVAHN-TAPPER & LANDBERG 1971).

SALZMAN et coll. wrote '. . . the symptoms, mainly secondary to irradiation of the upper respiratory tract segment, are tolerable and rarely require any interruption in the treatment schedule'. FULLER (1967) stated that 'complications of intensive irradiation for Hodgkin's disease . . . were rare'. NOBLER wrote 'in general, the local side effects are relatively mild and transient in nature and can be controlled with appropriate symptomatic medication'.

Certain side effects have attracted special interest, namely oesophagitis, irradiation pneumonitis, irradiation pericarditis, irradiation myelitis and hematologic complications.

KAPLAN (1962) and KAPLAN & ROSENBERG (1966) found that transient

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oesophagitis was common during treatment of the mediastinal region and that it sometimes persisted for a few weeks.

KAPLAN (1962) described a patient in whom massive mediastinal and cardiac involvement was present. The absorbed dose in the tumour was carried to 4 000 rad and the field had to include much of the pulmonary parenchyma on both sides. The patient died from pulmonary radiation fibrosis six years after treatment and no evidence of residual or recurrent Hodgkin's disease was found at autopsy. KAPLAN later (1966) remarked: 'approximately one third of patients experience a dry, irritating cough during the first few months following completion of mediastinal treatment, often associated with radiographic exaggeration of the pulmonary vascular markings indicative of paramediastinal radiation pneumonitis. By careful collimation and periodic field reshaping the severity of such reactions has been minimized and they usually have cleared promptly, leaving little or no functional incapacity and a normal chest radiograph'.

KAPLAN & ROSENBERG (1966) in three out of thirty-seven patients noted a transient acute pericarditis within the first 6 to 12 months after treatment, and in seven out of the thirty-seven patients reported 'mild, transient numbness and/or tingling in the fingers and toes, accentuated by flexing the neck (Lhermitte's sign), presumably attributable to a transient cervical or dorsal myelopathy'. None of the latter patients had paralysis.

KAPLAN (1966) found that 'cutaneous reactions during treatment are generally negligible and the later condition of the skin is excellent'.

SALZMAN et coll. (1964) found that 'radiation of the upper lymphoma field effected a fall in the white blood cell count to below 5 000 in 21 per cent of the patients'. KAPLAN (1966) stated 'leukopenia and thrombocytopenia occur during wide-field treatment but revert to normal within a few weeks or months in most instances'. KAPLAN & ROSENBERG (1966) reported that 'there have been no deaths due to hematopoietic injury'. They noticed no unusual susceptibility to bacterial infections, but several patients developed herpes zoster, which was sometimes unusually severe.

NOBLER stated: ... 'the only major problem which remains unresolved is bone-marrow depression. This tends to be minimal during a first course of irradiation, for example to the upper trunk lymph nodes, but somewhat more of a problem when this is followed by a second course of treatment to the major lymph node bearing areas of the lower trunk. A mild leukopenia, with the white blood count decreasing to 3 000 to 4 000 cells per mm^3, often develops during the first course of irradiation. This rapidly returns to normal, usually within 2 to 4 weeks. ... A thrombocytopenia parallels the leukopenia, with the lowest counts usually reaching no lower than 100 000 per mm^3, followed by a similar rise to normal levels. Anemia is rarely significant. In spite of the leukopenia and

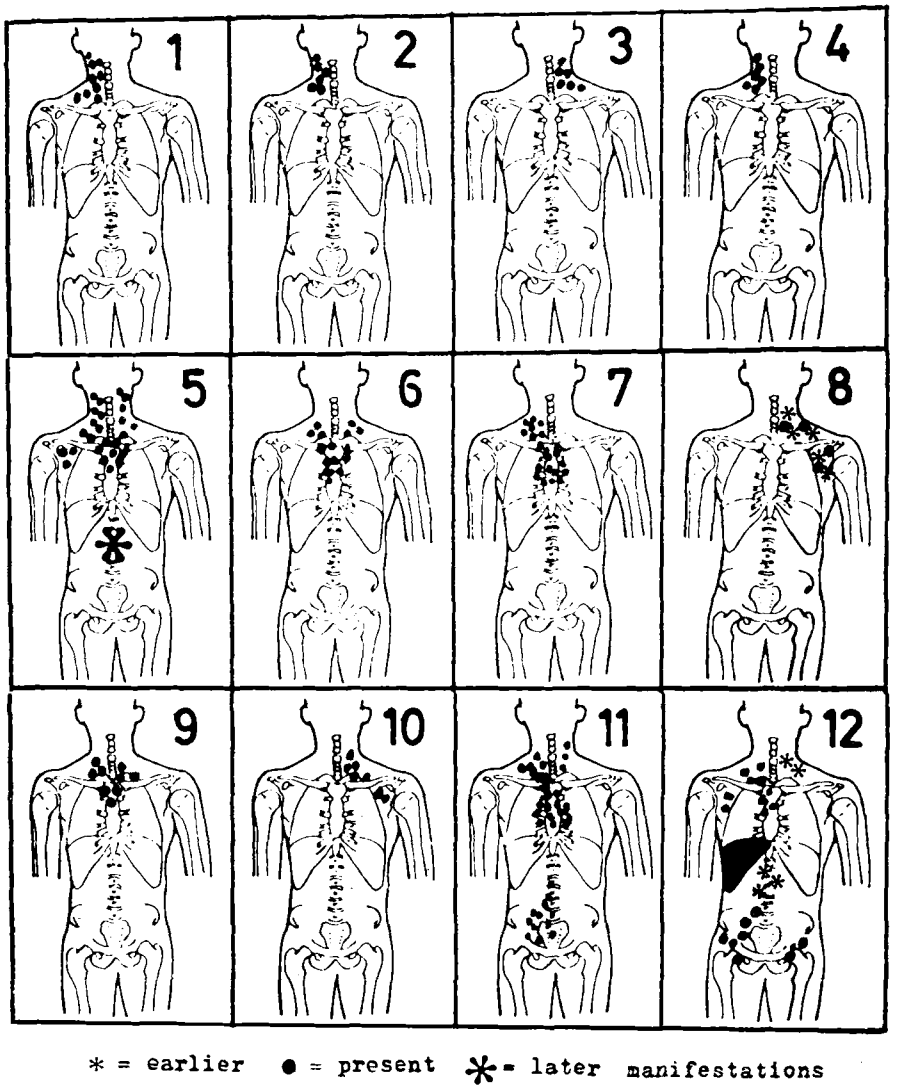

Fig. 1. Twelve patients with Hodgkin's disease. Clinical manifestations treated earlier, present at the beginning of mantle treatment, or diagnosed later.

thrombocytopenia, infections or bleeding episodes are exceedingly rare complications.'

JELLIFFE mentioned the possibility of inducing leukaemia in cured patients.

In patients with generalised disease, KAPLAN & ROSENBERG gave treatment both with the mantle technique and an 'inverted Y-shaped field' as well as ir-

radiation of the liver and spleen. Different regions were treated either in sequence or alternating over a period of 3 to 5 months.

This preliminary communication is concerned with the side effects and early results of mantle treatment of patients with Hodgkin's disease.

Material and Methods

Material. The series consisted of 12 patients (5 males and 7 females), aged 17 to 65 (median 25), with Hodgkin's disease, in whom mantle treatment was started before March 1st, 1968 (Fig. 1).

The histologic types of disease (LUKES et coll. 1966) were lymphocytic predominance in three (Nos. 4, 8 and 10), nodular sclerosis in two (Nos. 5 and 7) and mixed cellularity in the remaining seven patients. Before the first mantle treatment, roentgen examination of the chest had been performed in all the patients and of the skeleton in eight, lymphography in eleven, inferior cavography in eight, scintigraphy of the liver with colloidal ^{198}Au in all, and of the spleen with ^{197}Hg-BMHP in five patients. Epipharyngoscopy had been carried out in nine patients and microscopy of the sternal marrow aspirate in eleven patients. Fig. 1 shows the manifestations present at the first mantle treatment, as well as those treated earlier (Nos. 8 and 12) and diagnosed later (No. 5). Clinically, the disease was local in ten (Nos. 1 to 10) whereas intra-abdominal spread had been diagnosed in two (Nos. 11 and 12) patients. Mediastinal involvement had been detected in six of the patients and in three of these (Nos. 6, 7 and 11) the pulmonary hila were enlarged at the roentgen examination.

Dosage. The treatments were given according to the principles described by SVAHN-TAPPER (1970) and by SVAHN-TAPPER & LANDBERG (1971). In four of the patients (Nos. 8, 9, 10 and 11) beam flattening filters were used, whereas in the remaining eight patients the variation of the absorbed dose in the target was reduced solely by successive reductions of the fields.

Follow-up. After the conclusion of treatment the patients were seen once a month during the first half year and then every second month. The examination included roentgen examination of the chest and detailed blood tests.

Results and Discussion

Dosage. The irradiations were given with ^{60}Co at an SSD of 130 cm. The absorbed dose in the target was intended to correspond to 4 000 rad over 4 to 5 weeks. In a 5-days-a-week scheme, this means 200 to 160 rad in each of the fractions but to avoid severe nausea and fatigue more fractions were used in the present series.

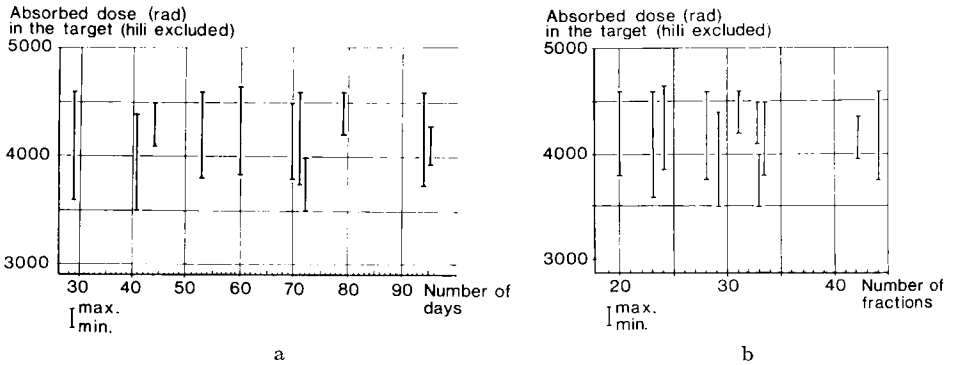

Fig. 2. Total absorbed dose (rad) in target (hilar region excluded) in the eleven patients given full mantle treatment, related to the number of days (a), and to the number of fractions given (b).

In eight of the twelve patients one field was irradiated with each fraction, the peak absorbed dose in the central beam being (mean) 225 rad. In four patients, both fields were irradiated with each fraction, the peak absorbed dose in the central beam then being (mean) 140 rad. Three patients were treated in one series over (mean) 38 days and with (mean) 28 fractions. The treatment in nine patients was given as a split course with about two thirds of the fractions in the first series and an interval of (mean) 34 days between the two series. For the split-course treatment, irradiation was given during (mean) 75 days with (mean) 31 fractions.

In one patient (No. 11), who also had abdominal lymphomas, a lower total dose was administered, whereas in the remaining eleven patients the full mantle treatment was given. Two of these eleven patients experienced however severe nausea during treatment and three complained of considerable weakness.

Fig. 2 sets out the total absorbed dose (rad) in the target for the eleven patients receiving full mantle treatment. The absorbed doses are related to the number of days (Fig. 2a) and to the number of fractions given (Fig. 2b). The absorbed doses were calculated on the assumption of homogeneous unit density tissue, and no regard was taken to the presence of lung tissue in the hilar regions. The maximum value never exceeded 4 650 rad and the minimum never fell below 3 500 rad in any of the patients. In the three patients in whom treatment was given in one series, the total number of days was 29, 41 and 44, respectively. The wide range in the number of days and the number of fractions, despite the fairly even level of the absorbed dose in the different patients, mirrors the individual tolerance. The absorbed dose in the spinal cord was 4 500 to 3 800 rad in a period of at least 4 weeks. The total absorbed dose in the eyes was less than 100 rad.

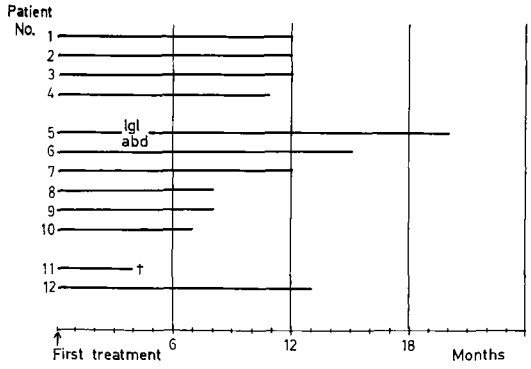

Fig. 3. Further clinical course in all the twelve patients after the beginning of mantle treatment; the plus sign denotes death.

Reactions of skin and mucous membranes. Four of the eleven patients who received full mantle treatment had symptoms of mucositis of the floor of the mouth, and two complained of symptoms of oesophagitis at the conclusion of treatment. These symptoms disappeared within a few weeks. None of the eleven patients had severe symptoms of laryngitis. In three patients, a cervical skin reaction extending into the axillary folds was noticed at the end of the treatment, and in all three the skin reaction was only dryness; in the remaining eight patients only a slight tanning was observed. All patients had radiation alopecia of the back of the head up to the level of the external occipital protuberance, and in the five males also of the lower part of the face, for 5 to 7 months after the end of treatment.

Follow-up. The further clinical course of the twelve patients is recorded in Fig. 3. In patient No. 11, the disease was advanced at the time of the first mantle treatment (see Fig. 1). It was decided to irradiate the abdominal lymphomas simultaneously. The response to treatment was poor, and the patient died (in high grade fever) 4 months after the first mantle treatment. Autopsy was not performed. In patient No. 5, repeat lymphography 4 months after the mantle treatment revealed abdominal lymphomas. Two months later this patient was given radiotherapy with an 'inverted Y-shaped field' technique up to an absorbed dose in the target of 4 000 rad. The remaining ten patients felt well and presented no further signs of disease about (mean) 12 months after the first mantle treatment. No local recurrences have been observed.

Two patients received therapy with cytostatics. In one (No. 12) such treatment was started 3 months after the first mantle treatment and in the other (No. 5) it was commenced 18 months after the first mantle treatment because of peripheral facial palsy which originally, but not later, was thought to be due to Hodgkin's disease.

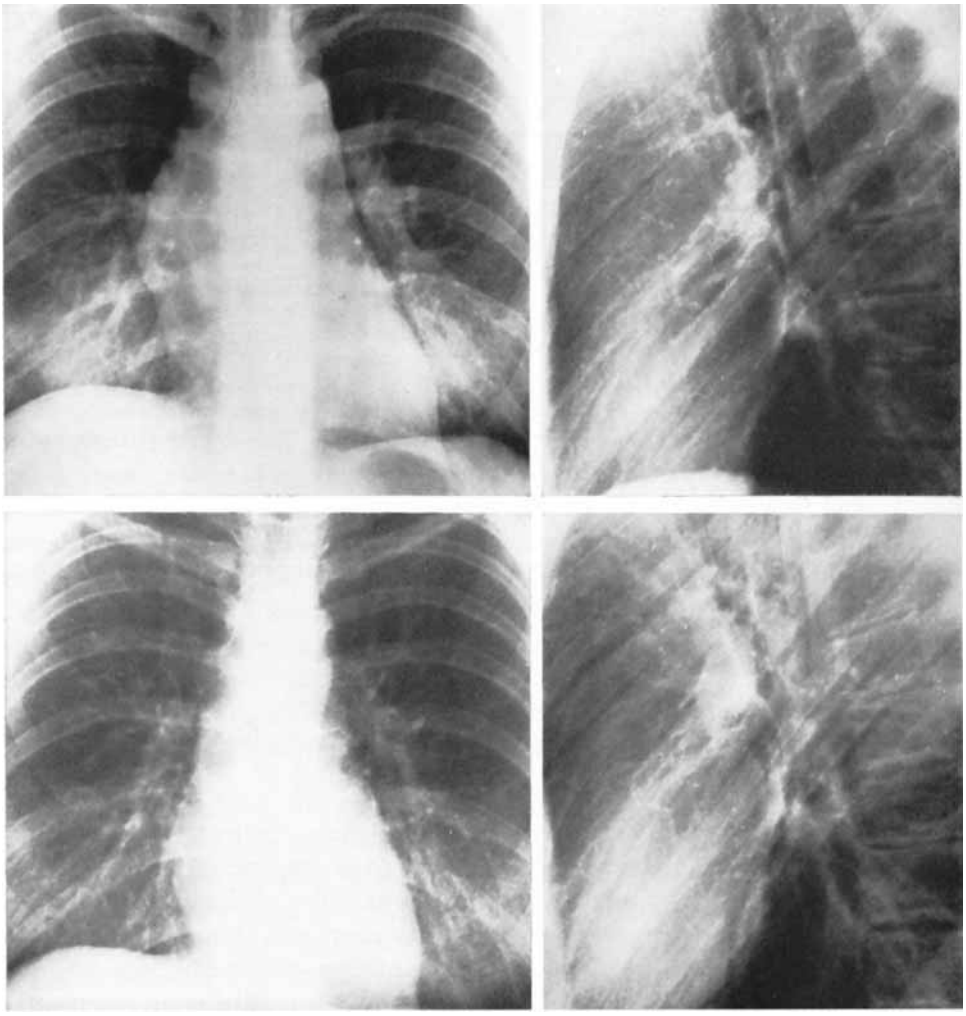

Fig. 4. Frontal and lateral roentgenograms of patient No. 6. *Upper views:* At the beginning of mantle treatment. Widening of superior mediastinum, especially to the right, with lymphomas in the right hilum. *Lower views:* At the end of mantle treatment. Marked regression in the size of the lymphomas but persistent widening of the superior mediastinum.

In no patient were there any symptoms of injury to the spinal cord nor to the cerebellum. One patient (No. 6) had moderate severe herpes zoster 3 months after the first mantle treatment. One patient (No. 8) maintained 10 months after the first treatment that some of her lower teeth had been injured by the therapy but this could not be objectively confirmed.

Cardiac reactions. No signs of pericarditis or any other cardiac conditions could be detected except in one patient (No. 1), who had continuous tachycardia. Electrocardiagrams were recorded in eight of the patients 8 to 15 months after the first mantle treatment and in three of these it had also been recorded before treatment. Two (Nos. 5 and 8) of the eight patients had slight ST-T-changes which however were considered to be of no pathologic significance. Patient No. 1 had tachycardia and an R:S ratio exceeding 1.0 in lead V_1, which might signify right ventricular hypertrophy. The ECG was completely normal in the other five patients.

Pulmonary reactions. Roentgenologic signs of radiation pneumonitis were present in nine of the eleven patients in whom the follow-up was at least 6 months. Pneumonitis was in general first diagnosed 3 to 5 months after the first mantle treatment at roentgen examination of the chest but in one patient (No. 12) as early as after a month. Four of the nine patients in whom roentgen examination had revealed pneumonitis had no symptoms, but five had cough and fever. The pulmonary conditions were treated with antibiotics and in four patients with steroids as well.

Fig. 4 (upper views) represents the chest roentgenograms of patient No. 6 at the beginning of mantle treatment. There was considerable widening of the superior mediastinum especially to the right with lymphomas in the right hilum. The lymphomas were smaller at the end of the treatment (Fig. 4, lower views) but there was still widening of the superior mediastinum. The maximum absorbed dose in the lung parenchyma in the hilar regions, corrected for the presence of lung tissue (SVAHN-TAPPER 1970, and SVAHN-TAPPER & LANDBERG 1971) had been 4 500 rad over 79 days and 31 fractions. Roentgen examination of the chest 5 months after the beginning of mantle treatment revealed marked pulmonary parenchymal changes due to pneumonitis as well as additional pleural changes and fibrosis on the right side (Fig. 5, upper views). The mediastinum with the trachea was displaced to the right. The patient had cough and fever and received antibiotic therapy. Roentgen examination 15 months after the beginning of mantle treatment disclosed further fibrosis (Fig. 5, lower views). The pneumonitis in this patient was the most severe pulmonary reaction observed in the present material. The patient improved and was then troubled by cough only on physical exertion. Of the nine patients in whom roentgen examination had indicated pneumonitis, six had been followed up for at least 10 months. The last roentgen examination revealed considerable fibrosis in three patients, only slight changes in two, and normal conditions in one patient. Two of the patients had neither symptoms nor signs of pneumonitis.

As has been shown previously (SVAHN-TAPPER 1970 and SVAHN-TAPPER &

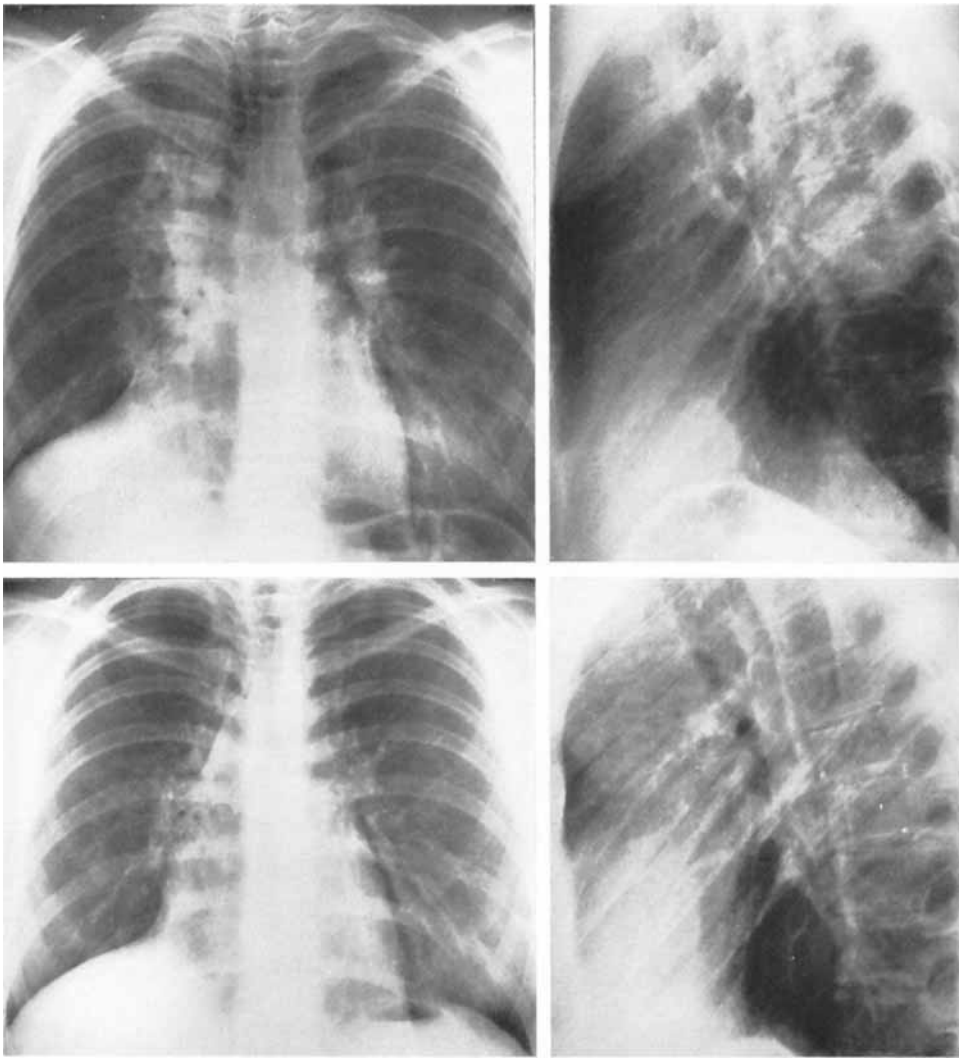

Fig. 5. Frontal and lateral roentgenograms of patient No. 6. *Upper views:* Five months after the beginning of mantle treatment. Central pneumonitis as well as pleural changes and fibrosis on the right side; mediastinum with trachea displaced to the right. *Lower views:* Fifteen months after the beginning of mantle treatment. Further fibrosis.

LANDBERG 1971) the absorbed dose in the hilar regions owing to the presence of lung tissue is higher than that calculated on the assumption of homogeneous unit density tissue. The maximum absorbed dose in the hilar regions was calculated for lung tissue (SVAHN-TAPPER & LANDBERG 1971) by phantom studies and

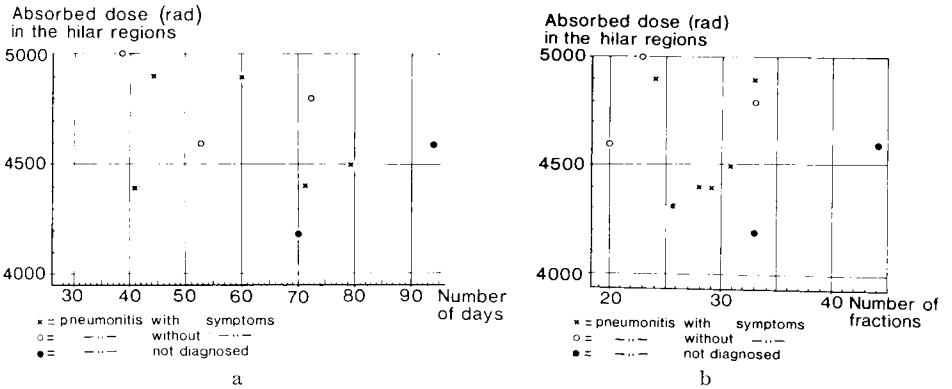

Fig. 6. Total maximum absorbed dose (rad) in the pulmonary parenchyma in the hilar regions, corrected for presence of lung tissue in ten patients given full mantle treatment (one patient excluded because of insufficient relevant dose measurements), in relation to the number of days (a) and to the number of fractions given (b).

by measurement of the exit absorbed dose in patients. These maximum absorbed doses in the hilar regions are given in Fig. 6 (patients Nos. 11 and 5 excluded because of too short observation time and too few measurements, respectively) in relation to the number of days (Fig. 6a) and the number of fractions given (Fig. 6b). They are presented as three types of reactions, namely roentgenologically demonstrated pneumonitis with or without symptoms and no diagnosed pneumonitis. The two patients in whom pneumonitis was not diagnosed had received treatment either over the longest period (94 days) or with the largest number of fractions (44), or had been given the lowest absorbed dose (4 200 rad). In the remaining eight patients, however, in whom the maximum absorbed dose in the hilar regions had been between 4 400 and 5 000 rad over 39 to 79 days and given in 20 to 33 fractions, no conclusions could be drawn about the type of fractionation and lung reaction. Nor was any correlation found between the presence of mediastinal lymphomas on roentgen examination before the treatment, or the histologic type of disease and the type of lung reaction, respectively. Roentgen examination revealed however pneumonits in all three of the patients in whom treatment was given in one series, and two of these also had symptoms.

Of eight patients given split-course treatment, two had neither symptoms nor signs of pneumonitis, whereas pneumonitis was roentgenologically demonstrated in six patients, three of whom also had symptoms.

Holsti & Vuorinen (1967) in an investigation of bronchial carcinoma reported that the incidence of radiation reactions in the lung within the dose range recorded as 3 100 to 4 000 R was smaller in the split-course group than

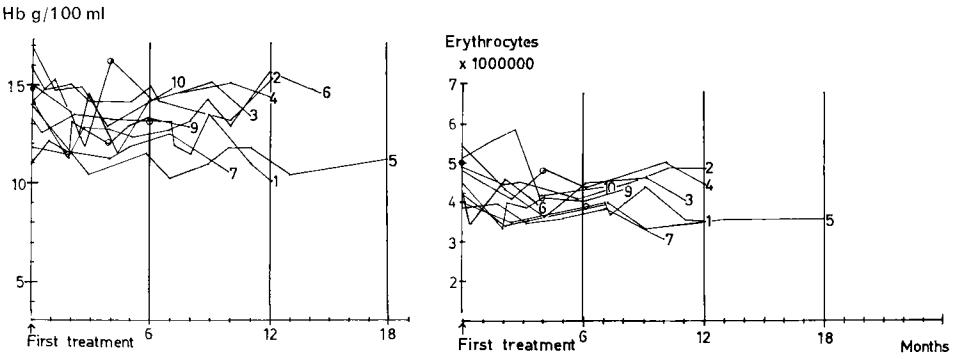

Fig. 7. Hemoglobin values (left) and erythrocyte counts (right) at the beginning of mantle treatment and later in nine patients with local disease not treated earlier. The small circles denote start of steroid treatment.

in the group of patients given continuous treatment. No precautions were taken in the present material to reduce the higher absorbed dose in the lung tissue of the hilar regions but the width of the field over part of the mediastinum is now diminished towards the end of treatment (SVAHN-TAPPER & LANDBERG 1971) to make the absorbed dose in the hilar regions equal to the absorbed dose in the other parts of the target. Furthermore, treatment is now always given as a split course.

In seven of the patients, dynamic spirometry (including vital capacity, forced expiratory volume in one second and maximal voluntary ventilation) was performed before as well as 4 to 15 months after the beginning of mantle treatment.

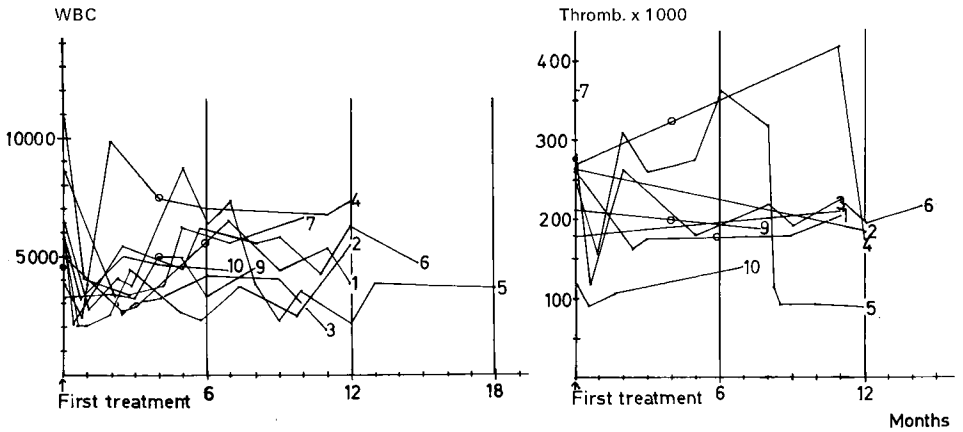

Fig. 8. Leucocyte counts (left) and thrombocyte counts (right) at the beginning of mantle treatment and later in nine patients with local disease not treated earlier. The small circles denote start of steroid treatment.

In three of these patients (Nos. 3, 5 and 12) the values obtained before the treatments were normal and had not changed on examinations performed 12, 4 and 13 months, respectively, after the treatment. In a further three of the patients (Nos. 6, 8 and 10) there were slight restrictive changes at the last examinations made 15, 10 and 7 months respectively, after the treatment (the vital capacity decreased by 0.9 to 1.2 liter, in two of them combined with a decrease in the maximal voluntary ventilation by 30 to 40 liter/minute). The last patient examined (No. 4) had from the very beginning a lowered (1 liter) vital capacity, which 11 months after the beginning of mantle treatment had not changed, while the maximal voluntary ventilation had decreased by about 25 liter/minute.

Except for the symptoms during the acute stage of irradiation pneumonitis, the lung reactions resulted only in cough on exertion in some patients, but never in subjective respiratory incapacity. This corresponds well with the relatively moderate decrease in the spirometric values.

Depression of blood values. Figs 7 and 8 give the pre-, per- and post-therapeutic hemoglobin values and respectively the erythrocyte, leucocyte and thrombocyte counts in the nine patients with local disease who had received no treatment before they were given treatment according to the mantle technique. All the four types of values generally fell during treatment but afterwards gradually rose to plateaux values only somewhat below the original values. All patients were given iron and vitamin preparations during and after the mantle treatment. Steroids were administered to four patients for pneumonitis. No blood transfusions or cytostatics were given during the intervals shown in Figs 7 and 8. Patient No. 5 was treated with an 'inverted Y-shaped field' technique, started 6 months after the beginning of the mantle treatment but, except for thrombocytopenia, the blood values remained fairly constant.

Acknowledgement

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SUMMARY

A preliminary account of side effects and early results in twelve patients with Hodgkin's disease given radiotherapy with a mantle technique is presented. Radiation pneumonitis developed in most patients. Other side effects have been of less importance. No further manifestations were observed in nine out of ten patients with clinically local disease followed up for on the average 12 months.

ZUSAMMENFASSUNG

Es wird ein vorläufiger Bericht über die Mantelbestrahlungsmethode bei zwölf Patienten mit Hodgkinscher Erkrankung, einschliesslich der Resultate und ungewünschten Nebenwirkungen, abgegeben. Strahlenpneumonie erfolgte bei den meisten Patienten und andere Nebenwirkungen waren von untergeordneter Bedeutung. Nach ungefähr einem Jahr hatten neun von zehn Patienten mit nur lokaler Erkrankung keinerlei aktive Symptome.

RÉSUMÉ

Compte-rendu préliminaire des effets secondaires et des résultats précoces de l'irradiation par la technique en manteau chez douze malades atteints de maladie de Hodgkin. La plupart des malades ont eu une pneumopathie radiothérapique. Les autres effets secondaires ont été moins importants. Il n'y a pas eu d'autres manifestations chez neuf des dix malades présentant une atteinte cliniquement localisée et suivis en moyenne pendant 12 mois.

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