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PODOPHYLLIN DERIVATIVES SPG 827 AND SPI 77* IN THE TREATMENT OF ADVANCED CANCER

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We have now treated 72 patients suffering from advanced cancer with the podophyllin derivatives SPG 827 and SPI 77, using these cancer chemotherapeutic agents either alone or in various combinations with radiotherapy and other cytostatic drugs. Toxic side-effects have not been severe. On the whole, the value of these podophyllin derivatives in the treatment of advanced cancer has been rather doubtful, especially when used alone. In combination with radiotherapy and other cytostatic drugs some remissions have been obtained. Although our results have been disappointing we feel they should be recorded.

Some Published Observations

Sullivan *et al.*[1] (1947) observed that podophyllin caused mitosis to become arrested during metaphase, and Cerletti *et al.*[2] (1959) reported that podophyllin glucosides showed a similar qualitative effect in arresting mitosis but with a better therapeutic index. Emmenegger *et al.*[3] (1961) found that gastro-intestinal absorption of the benzylidene compounds of the podophyllin glucosides was more effective than that of the natural glucoside. The podophyllin derivative SPG 827 consists of the benzylidene compounds of all the glucosides of *Podophyllum emodi;* 70% of the mixture is podophyllotoxin-beta-D-benzylidene-glucoside. The podophyllin derivative SPI 77 is the ethyl hydroxide of podophyllic acid.

At the Sandoz laboratories[4] the effects of these two drugs have been studied *in vitro* and *in vivo* in mice. Therapeutic effects were obtained in Ehrlich's ascites, leukaemia 1210, and sarcoma 37. Toxicity studies have been performed on rats, cats, dogs and monkeys. In monkeys, doses of up to 30 mg./kg./day for 110 days produced no toxic effects, but doses of more than 45 mg./kg./day caused anorexia, cachexia, diarrhoea, and occasional loss of hair, as well as leukopenia without anaemia. Necrotic foci were found in the liver and myocardium when SPI 77 was given in massive doses of 60-100 mg./kg./day for 12-16 days. SPI 77 was found to be excreted mainly by the kidneys. In man, SPI 77 is excreted in the urine—10% after 6 hours and 40% after 3 days. SPG 827 given orally is excreted mainly in the bile—50% after 48 hours. Whether these podophyllin derivatives or antimitotic drugs act as antimetabolites is unknown.

Material and Method

Of the 72 patients treated and analysed, 47 were White and 25 non-White; 54 were males and 18 females; their ages varied from 10 to 76 years.

Histological confirmation of the diagnosis was obtained in all 72 patients, and the presence of distal metastases was established by clinical observation or radiological demonstration.

An analysis of our 72 cases showed that 28 patients had received concomitant radiotherapy to a single symptomatic lesion (including 3 patients who had received radical radiotherapy during the time that they were on treatment with SPG 827 and SPI 77, namely 1 with myosarcoma, 1 with oesophageal carcinoma and 1 with rectal carcinoma, as well as 2 patients who had received radical radiotherapy just before SPG 827 was administered, namely, 1 with fibrosarcoma and 1 with oesophageal carcinoma); 22 patients had received radical radiotherapy more than 3 months before the commencement of SPG-827 and SPI-77 therapy; 17 patients had previously received other forms of cancer chemotherapy; and 5 patients had received concomitant 'endoxan' and SPG-827 therapy.

SPG 827 was given in divided daily oral doses either in the form of capsules or as drops placed on the patient's tongue. The smallest daily dose was 25 mg./day and the largest 500 mg./day. The largest total dose was 92,175 mg.

SPI 77 was given in 250 ml. of 5% glucose solution as a rapid intravenous infusion, initially either once daily or once every second day, and later once every week. The smallest dose was 400 mg./day and the largest 2,000 mg./day. The largest total dose was 17,600 mg.

Of the 72 patients, 36 received only SPG 827 and 4 only SPI 77, while 32 patients received both SPG 827 and SPI 77. The largest total combined dose was 106,975 mg.

Differential blood counts were obtained at the beginning of therapy and in most cases twice weekly thereafter. Blood-urea and liver-function tests were undertaken at the beginning of treatment and thereafter as required or indicated. Catalase determinations were made in 4 cases. All the patients were weighed at regular intervals, and measurable lesions photographed.

RESULTS

Although many of our patients experienced symptomatic improvement in the absence of objective improvement, such improvement was unfortunately of short duration—

TABLE I. COMPARISON OF RESULTS WITH TOTALS OF THOSE PREVIOUSLY PUBLISHED

	Literature		*Pretoria*	
Site of neoplasm	*Number of cases*	*Objective improvement*	*Number of cases*	*Objective improvement*
Tongue ..	—	—	1	0
Salivary gland	—	—	1	0
Oesophagus ..	20	6	14	1
Stomach ..	73	8	6	0
Colon	51	4	7	0
Hepatoma ..	—	—	11	0
Larynx ..	—	—	1	0
Antrum ..	—	—	1	0
Bronchus and lung ..	72	6	3	0
Pleura (mesothelioma) ..	—	—	6	2
Breast	96	19	5	1
Kidney ..	17	3	2	1
Male genitals	15	2	4	3
Uterus ..	22	0	2	1
Thyroid ..	—	—	1	0
Sarcoma ..	16	1	5	2
Neuroblastoma	—	—	1	1
Melanoma ..	—	—	1	0

*The podophyllin derivatives have been supplied to us for research purposes by Sandoz Laboratories, Switzerland.

†In receipt of a research grant from the National Cancer Association of South Africa.

TABLE II. DETAILS OF 12 PATIENTS WHO RESPONDED TO SPG 827 AND SPI 77

Case No.	Primary site and complications	Age and Sex	Previous therapy	P.S. Before	P.S. After	Details SPG (mg./day)	Total SPG (mg.)	Details SPI (mg.)	Total SPI (mg.)	Concomitant therapy	Evidence of remission	Duration of remission
1	Pleural mesothelioma	52—M	Nil	C	A	75/d — 4d 150/d — 2d 225/d — 3d 150/d — 4d 225/d — 54d 300/d — 253d 150/d — 15d **Total — 335d**	300 300 675 600 12,150 75,900 2,250 **92,175**	400 × 3 800 × 4 1,600 × 2 800 × 1 1,600 × 4 **Total — 36d**	1,200 3,200 3,200 800 6,400 **14,800**	DXT 1,000 rads—pleura. Co-60 3,150 rads in 4 weeks to lungs and pleura	Dyspnoeic. Bedridden patient back to manual labour	10 months
2	Pleural mesothelioma	72—M	Nil	C	B	— **Total — 62d**	— **11,025**	—	—	Co-60 3,200 rads in 4 wks. Endoxan 3,400 mg.	—	30 days. Follow-up lost
3	Breast carcinoma with bone metastases	36—F	DXT. Oophorectomy. Endoxan. Androgen	B	A	75/d — 4d 125/d — 47d 150/d — 42d 225/d — 20d **Total — 113d**	300 5,875 6,300 4,500 **16,975**	800 × 6 600 × 2 800 × 1 1,000 × 1 **Total — 95d**	4,800 1,200 800 1,000 **7,800**	DXT 1,000 rads—1 week—thoracic vertebrae	Disappearance of skin nodules	90 days. Still in remission
4	Kidney — nephroblastoma with lung, liver, mesenteric & bladder metastases	11—F	DXT	D	B	— **Total — 141d**	— **10,575**	600 × 8 800 × 6 1,000 × 2 **Total — 141d**	4,800 4,800 2,000 **11,600**	Endoxan 100 mg. 4×/w/os for 16 weeks	Clearing of lung met. Decrease in hepatomegaly. Disappearance of ascites & oedema	102 days. Still in remission
5	Prostatic carcinoma with metastases of bone and pelvic soft tissue	77—M	Tace	D	B	— **Total — 169d**	— **16,675**	800 × 17 2,000 × 2 **Total — 169d**	13,600 4,000 **17,600**	—	Decrease of palp. pelvic tumor. Urinary obstr. alleviated	150 days. Still in remission
6	Prostatic carcinoma	67—M	Tace	C	B	100/d — 15d 75/d — 94d **Total — 109d**	1,500 7,050 **8,550**	—	—	—	Decrease in size of local carcinoma	104 days. Still in remission
7	Testicle — seminoma with chest and hepatic metastases	33—M	DXT. Endoxan	B	A	100/d — 78d 150/d — 85d **Total — 163d**	7,800 12,750 **20,550**	800 × 4 1,000 × 2 1,200 × 1 **Total — 163d**	3,200 2,000 1,200 **6,400**	—	Disappearance of measurable met. Gained 40 lb.	150 days. Still in remission
8	Neuroblastoma with multiple bone metastases	14—M	Co-60	C	B	— **Total — 78d**	— **5,850**	600 × 5 800 × 2 1,000 × 1 600 × 5 **Total — 78d**	3,000 1,600 1,000 3,000 **8,600**	Endoxan 100 mg./day/os for 78 days	Increased mobility. Decreased muscle spasm	64 days. Still in remission
9	Stomach — myosarcoma with abdominal metastases	63—M	Nil	C	A	50/d — 1d 100/d — 1d 125/d — 1d 150/d — 1d 125/d — 115d 150/d — 502d **Total — 621d**	50 100 125 150 14,375 75,300 **90,100**	—	—	Co-60 1,500 rads in 1 week on 7 occasions: total 10,500 rads in 621 days	Palpable tumour and hepatomegaly disappeared. Weight gain	600 days. Still in remission
10	Lower ligament—myosarcoma with metastases in thigh, groin and scrotum	26—M	Nil	D	B	75/d — 6d 150/d — 8d 225/d — 7d 300/d — 8d 375/d — 53d **Total — 82d**	450 1,200 1,575 2,400 19,875 **25,500**	—	—	DXT 3,200 rads in 3 weeks to tumour and glands	Disappearance of measurable tumour. Gained 22 lb.	70 days. Follow-up lost
11	Oesophageal carcinoma	76—F	Co-60. 5,800 rads/4 weeks completed just before SPG begun	C	B	33/d — 10d 50/d — 14d 100/d — 81d **Total — 105d**	330 700 8,100 **9,130**	—	—	—	Improved appetite. Gained 10 lb.	85 days. Still in remission
12	Cervical carcinoma	75—F	Radium. DXT. Co-60	D	C	— **Total — 60d**	— **4,500**	600 × 5 800 × 1 1,000 × 3 **Total — 60d**	3,000 800 3,000 **6,800**	DXT 2,000 rads in 2 weeks	Temporary decrease in abdominal mass	45 days

PS = present status A = normal activity B = limited activity C = unable to care for personal means D = bedridden (very ill patient) d = day(s)

never longer than 6 weeks. Out of the total of 72 cases there were, however, 12 in which not only did the patient experience subjective improvement but objective improvement of a measurable nature also occurred (Figs. 1, 2, 3 and 4).

In Table I we have compared our results with those found in the literature. In Table II we give details of the 12 patients who responded to SPG-827 and SPI-77 therapy. Clinically we could find no evidence of radiosensitization or radiopotentiation by the use of these cancer chemotherapeutic agents. None of these patients who had previously received radical radiotherapy showed any undue reactions nor was there any unexpected hyperpigmentation to be observed in the field of irradiation.

Toxicity

SPG 827 causes diarrhoea, and this has proved to be the limiting factor in the administration of this cytostatic drug. Many patients complained of nausea, but otherwise no other signs of toxicity were observed. Even long-term therapy has not affected measurable bone-marrow function; e.g. the blood count of a patient (case 9, Table II) with sarcoma of the stomach who had received 90,100 mg. in 621 days was Hb. 16·8 G./100 ml. (i.e. 113%) and leukocytes 12,000 per cu.mm., and his liver-function tests had returned to normal.

Large doses of intravenous infusions of SPI 77 caused some bizzare subjective sensations, which lasted only for a minute or more and varied from patient to patient. Large doses have caused some changes in the leukocyte count.

Analyses of Blood-cell Counts in 4 Patients on SPI-77 Therapy

In 4 patients the normal dosage of SPI 77 was not adhered to; much larger and more frequent doses were given. These patients were all bedridden and very ill. Their differential blood counts are of interest. They are recorded in Tables III, IV, V and VI, with the dosage of SPI 77.

Table III contains these details in the case of a male aged 52 (case 1 in Table II), bedridden with a pleural mesothelioma, hepatomegaly and abdominal metastases. The record is from the 318th to the 355th day, when he died.

Table IV refers to a male aged 53, bedridden with anaplastic adenocarcinoma of the pharynx with metastases in the spinal column, paraplegia, and measurable metastases on the abdominal wall. The record concerns the last 27 days of his life, when he was on SPI-77 treatment.

Table V refers to a male aged 60 with carcinoma of the stomach resistant to combined Co-60 and 5-fluorouracil therapy. This patient developed a complete gastrointestinal obstruction. Operation was out of the question. He was treated with SPI 77 and Co-60 in the hope of relieving the obstruction. The Co-60 was administered from the 1st to the 5th day—200r per day for 5 days over the upper abdomen—and repeated from the 8th to the 12th day. The record is for the last 18 days of his life, during which he received some relief. The last blood count was obtained ½ an hour before he died.

Table VI refers to a male aged 63 with advanced carcinoma of the larynx which had completely infiltrated the neck and ulcerated to the outside. The patient was also unable to swallow. The record concerns the last 18 days of his life.

The interesting features about these blood counts are (1) the fall in the leukocyte counts, with a tendency to recover, and (2) the constant rise in the staff-cell counts, which run a parallel course in all four of these patients on large doses of SPI 77.

TABLE III. BLOOD COUNTS OF MAN AGED 52 WITH PLEURAL MESOTHELIOMA AND METASTASES, ON INTENSIVE SPI-77 THERAPY

Treatment day	*Dose SPI 77*	*Hb.%*	*WBC*	*Blood count*						
				S	*P*	*L*	*M*	*E*	*B*	*Pl*
318th	—	81·8	7,000	—	85	12	3	—	—	N
320th	400	—	—	—	—	—	—	—	—	—
323rd	400	81·0	5,700	0	83	7	9	0	1	N
324th	400	—	—	—	—	—	—	—	—	—
325th	400	—	—	—	—	—	—	—	—	—
326th	400	—	—	—	—	—	—	—	—	—
327th	—	79·0	4,300	—	—	—	—	—	—	—
328th	800	—	—	—	—	—	—	—	—	—
330th	800	79·0	6,700	0	93	6	1	0	0	N
331st	800	—	—	—	—	—	—	—	—	—
332nd	800	—	—	—	—	—	—	—	—	—
333rd	1,600	—	—	—	—	—	—	—	—	—
334th	1,600	—	—	—	—	—	—	—	—	—
337th	1,600	—	—	—	—	—	—	—	—	—
338th	1,600	—	—	—	—	—	—	—	—	—
339th	—	74·0	4,200	—	—	—	—	—	—	—
340th	1,600	—	—	—	—	—	—	—	—	—
341st	1,600	—	—	—	—	—	—	—	—	—
344th	—	68·5	8,300	16	78	2	4	0	0	N
348th	—	72·0	3,100	—	90	2	8	0	0	N
352nd	—	67·0	6,300	—	96	2	2	—	—	N
355th	**Died**									

In Tables III, IV, V and VI Hb=haemoglobin. WBC=white blood cells. S=staff cells. P=polymorphs. L=lymphocytes. M=monocytes. E=eosinophils. B=basophils. Pl=platelets.

TABLE IV. BLOOD COUNTS OF MAN AGED 53 WITH ANAPLASTIC ADENOCARCINOMA OF PHARYNX AND METASTASES, ON INTENSIVE SPI-77 THERAPY

*Treatment day**	*Dose SPI 77*	*Hb.%*	*WBC*	*Blood count*						
				S	*P*	*L*	*M*	*E*	*B*	*Pl*
1st	400	92·0	8,200	0	60	32	6	2	0	N
2nd	400	—	—	—	—	—	—	—	—	—
4th	400	—	—	—	—	—	—	—	—	—
5th	400	91·5	8,700	0	70	21	6	2	1	N
7th	400	—	—	—	—	—	—	—	—	—
8th	800	—	—	—	—	—	—	—	—	—
10th	800	82·5	10,700	0	80	14	4	1	1	N
11th	800	—	—	—	—	—	—	—	—	—
12th	800	—	—	—	—	—	—	—	—	—
13th	1,600	—	—	—	—	—	—	—	—	—
14th	1,600	70·5	8,200	0	93	6	1	0	0	N
17th	800	—	—	—	—	—	—	—	—	—
20th	1,600	68·5	4,100	12	72	16	0	0	0	N
21st	1,600	—	—	—	—	—	—	—	—	—
24th	—	70·5	4,900	14	70	16	0	0	0	N
25th	—	68·5	5,900	10	61	18	10	0	0	N
27th	**Died**									

*No SPG 827 given

TABLE V. BLOOD COUNTS OF MAN AGED 60 WITH CARCINOMA OF STOMACH AND COMPLETE GASTRO-INTESTINAL OBSTRUCTION, ON INTENSIVE SPI-77 THERAPY

*Treatment day**	*Dose SPI 77*	*Hb.%*	*WBC*	*Blood count*						
				S	*P*	*L*	*M*	*E*	*B*	*Pl*
1st	800	127·0	5,700	—	76	18	4	2	0	N
4th	2,000	—	—	—	—	—	—	—	—	—
5th	2,000	—	—	—	—	—	—	—	—	—
6th	2,000	—	—	—	—	—	—	—	—	—
7th	2,000	—	—	—	—	—	—	—	—	—
8th	1,000	—	3,300	—	80	12	8	0	0	N
10th	—	—	2,300	—	—	—	—	—	—	—
14th	—	101·5	1,700	14	52	24	8	2	—	N
16th	—	—	2,000	16	62	12	10	0	—	N
18th	**Died**	93·0	900	—	—	—	—	—	—	—

*No SPG 827 given.

TABLE VI. BLOOD COUNTS OF MAN AGED 63 WITH ADVANCED CARCINOMA OF LARYNX THAT HAD ULCERATED TO OUTSIDE OF NECK, ON INTENSIVE SPI-77 THERAPY

*Treatment day**	*Dose SPI 77*	*Hb.%*	*WBC*	*Blood count*						
				S	*P*	*L*	*M*	*E*	*B*	*Pl*
1st	1,000	98·5	10,000	—	80	20	—	—	—	N
2nd	1 000	—	—	—	—	—	—	—	—	—
3rd	1,000	98·5	12,000	—	71	22	6	1	—	N
4th	1,000	—	—	—	—	—	—	—	—	—
6th	1,000	—	—	—	—	—	—	—	—	—
7th	1,000	—	—	—	—	—	—	—	—	—
8th	—	96·0	8,500	—	77	14	9	—	—	N
9th	1,000	—	—	—	—	—	—	—	—	—
10th	2,000	—	—	—	—	—	—	—	—	—
12th	1,000	—	—	—	—	—	—	—	—	—
14th	—	82·5	4,500	11	70	16	3	—	—	N
17th	—	—	5,000	—	—	—	—	—	—	—
18th	**Died**									

*No SPG 827 given.

Catalase Determinations in 4 Patients

Formation of the enzyme catalase is inhibited by the toxohormone excreted by tumour tissue.[5] Change in skin catalase concentration seems to be of prognostic importance in patients with tumours.[6] Catalase determinations were obtained on 4 patients. Volkman's-spoon skin specimens were used and measured by a titrometric method. Results are shown in Table VII.

TABLE VII. CATALASE DETERMINATIONS IN 4 PATIENTS UNDER TREATMENT WITH SPI AND SPG

Case	*Days of treatment*	*Kat. F. value*	*Clinical progress*
No. 3	51	202·4	Improved
F. 36 years	53	210·0	Improved
Breast Ca.	99	229·1	Improved
No. 11..	1	185·4	
F. 76 years	4	206·0	Improved
Oesophageal Ca.	81	214·6	Improved
No. 12..	1	111·0	
F. 75 years	15	132·6	Improved
Cervical Ca.			
No. 72	5	255·7	
M. 64 years	8	157·0	Worse
Bronchial Ca.	12	—	Died

Example of Objective Remission

Case 4 in Table II, an 11-year-old girl, was referred on 5 December 1961 for postoperative radiotherapy for an extensive nephroblastoma of the left kidney with metastases to the para-aortic lymph nodes and the left lobe of the liver, proved histologically. During operation 400 mg. of 'endoxan' were administered intravenously.

Routine blood counts were performed before radiotherapy was given and during the treatment. An X-ray of the chest revealed no lung metastases. Deep X-ray therapy was administered through two opposing fields to include the tumour bed, the left lobe of the liver, and the para-aortic lymph nodes. A tumour dose of 3,000r in 3 weeks was given. The patient stood the treatment well; but from January 1962 to January 1963 she had a chequered career, and, in spite of remissions on endoxan and deep X-ray therapy, on the whole there was a marked downward trend in the general health of the patient.

On 16 January 1963 she presented with enlarged abdominal lymph nodes and ascites, and 750 ml. of blood-stained fluid were aspirated. In spite of deep X-ray therapy the mass in the abdomen became bigger and the abdomen filled up with fluid. The patient suffered severe pains. There were now oedema of the ankles and enlarged veins on the abdomen and over the chest wall (Fig. 1), and X-rays of the chest revealed large cannon-ball metastases in the right lung (Fig. 3). The patient was so weak that she could not sit up and her life was in danger. Further X-ray therapy was inadvisable and she was

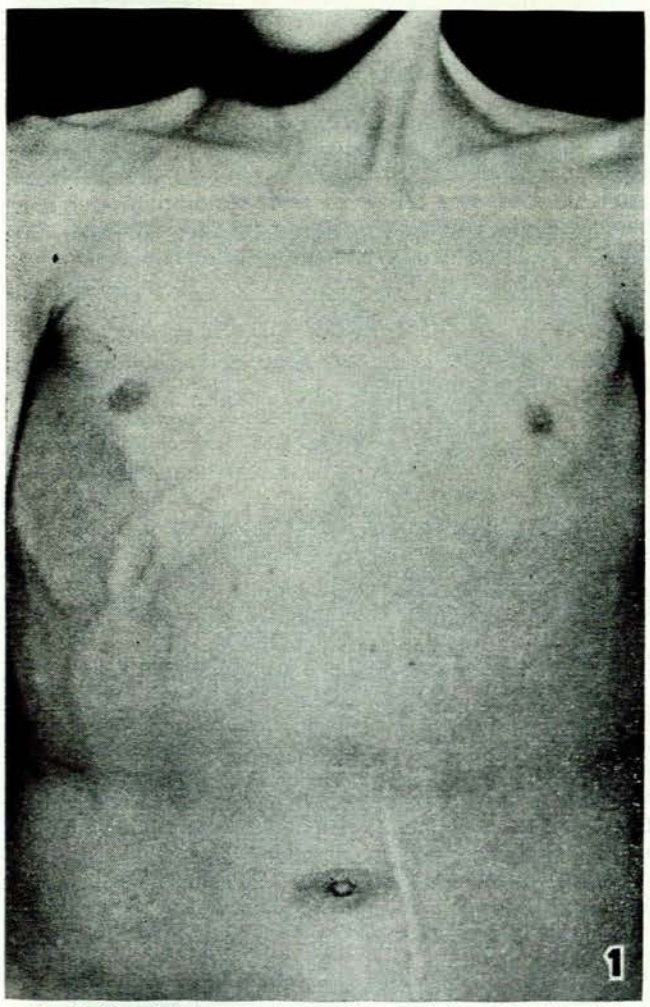

Fig. 1. Case 4 before treatment with podophyllin derivatives. Enlarged vessels on chest and abdomen.

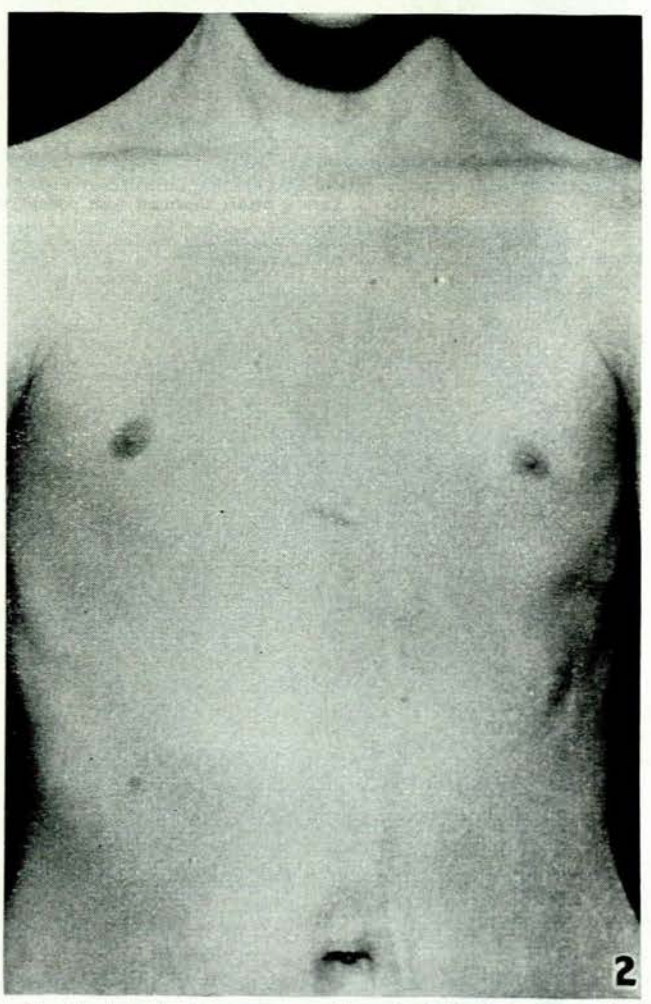

Fig. 2. Case 4 after treatment with podophyllin derivatives. Disappearance of enlarged vessels.

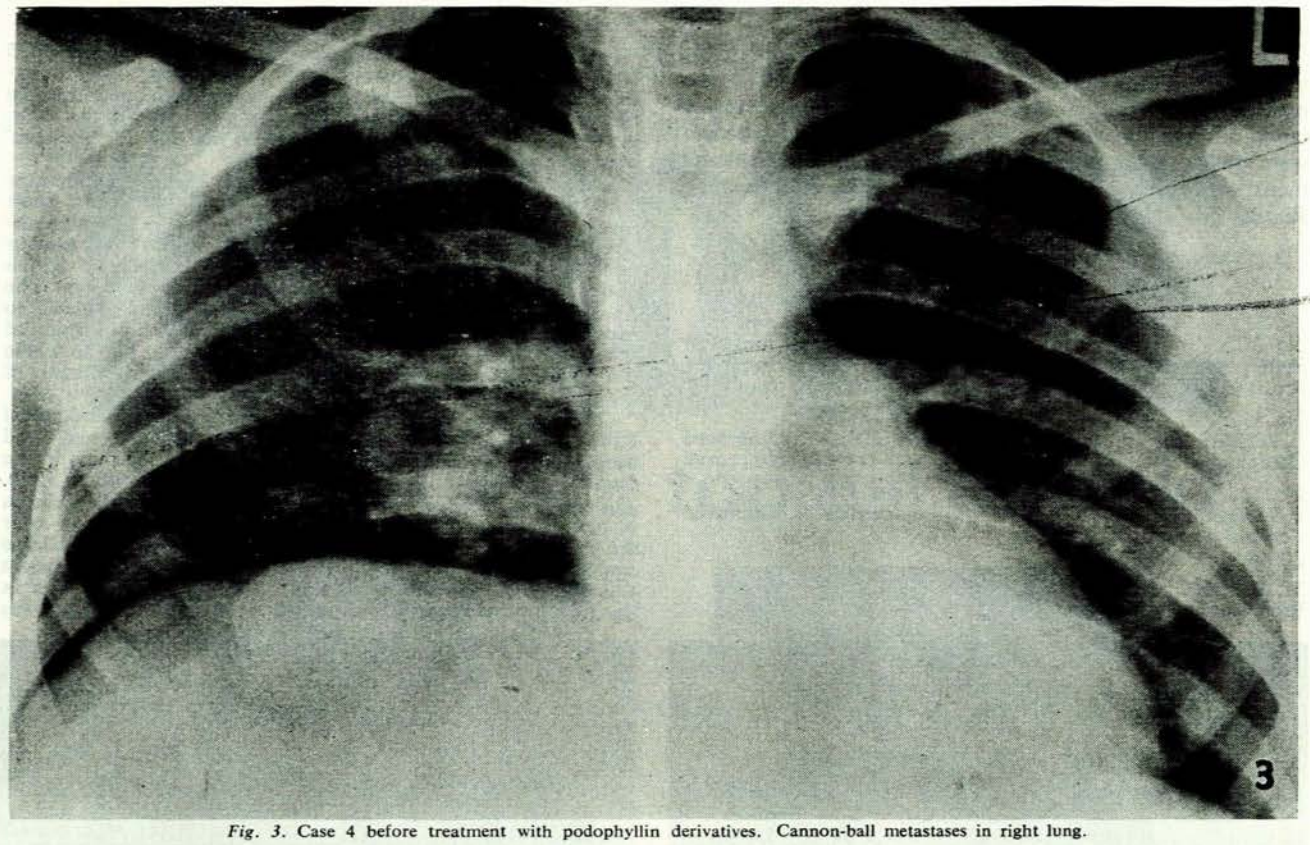

Fig. 3. Case 4 before treatment with podophyllin derivatives. Cannon-ball metastases in right lung.

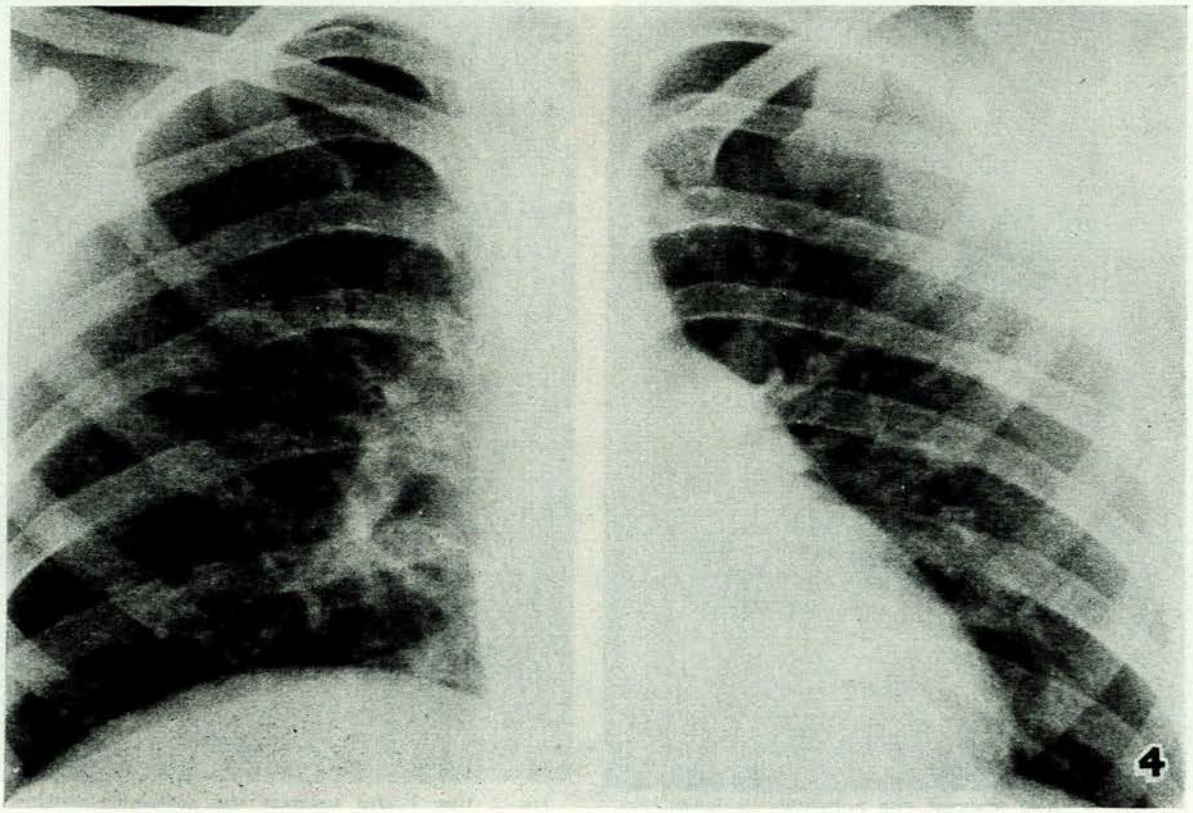

Fig. 4. Case 4 after treatment with podophyllin derivatives. Disappearance of cannon-ball metastases.

put on the following cancer chemotherapeutic drugs from 31 January 1963: (1) endoxan, 500 mg./week, (2) SPG 827, 1 capsule *t.d.s.*, and (3) SPI 77, 600 mg. intravenously once a week.

The patient was re-examined at weekly intervals and routine blood examinations and liver-function tests were performed. After a week there was a dramatic improvement in her condition. The ascites and oedema of the ankles started to subside and the liver was much smaller. A month later there was no ascites, enlarged vessels, or swelling of the ankles (Fig. 2). The enlarged liver continued to shrink, the abdominal metastases were much smaller, and the patient was up and about. X-rays of the lungs revealed no signs of any metastases (Fig. 4).

DISCUSSION

Hubacher[7] has published a preliminary report on 145 patients treated with 6 - 12 capsules of SPG 827 per day (1 capsule = 25 mg.) and/or 2 - 3 ampoules of SPI 77 per week (1 ampoule = 200 mg.). He states that he has seen no blood dyscrasia and only one case of eczema, despite the fact that he has used this therapy chiefly as an adjunct to radiotherapy. In some of our patients who were very ill and were given large doses of SPI 77 in the hope of obtaining some effect in very far advanced neoplasm, skin toxicity[8] and probable haematological toxicity were demonstrated.

Some 2,000 patients have received SPG 827 and SPI 77 in various clinics in the world. Only 606 have been evaluated to date and the results in these are compared to our results in this study. In Table I 382 of the 606 patients evaluated by Sandoz are represented. The remaining cases not shown in Table I consisted of neoplasms of the following sites: reticulo-endothelium 40, ear nose throat 31, brain 27, ovary 25, skin 21, bladder 14, various 66. Our results are comparable to them, showing improvement in 12/72 as compared to 11% (67/606) of the groups evaluated by Sandoz.

It is still hoped that these drugs will be useful in tumours resistant to other therapy. It seems evident that they cannot be considered as drugs of first choice in most common tumours. Although their low toxicity makes the podophyllin derivatives easy to use as adjuvant to surgery it must be noted that the American group studying this subject have concluded: 'In the future, therefore, only those agents which have been found to cause objective remission in a minimum of 15% of patients with advanced disease will be studied as adjuvant to curative surgery'.

We could find no evidence of potentiation of radiation with these drugs as we have found with 5-fluorouracil.[9-11] They can therefore be administered without producing the usual added toxic effects that result from the administration of alkylating agents and most antimetabolites during radiotherapy.

In the cases where catalase determinations were performed the values recorded are indicative of the value of response. There is, however, no evidence to suppose that the podophyllins specifically inhibit toxohormone excretion by tumours.

SUMMARY

Twelve out of 72 patients with advanced malignant neoplasms treated with SPG 827 and/or SPI 77 showed objective measurable improvement. The type of objective improvement obtained is illustrated. Four patients were given very large doses of SPI 77 and only in these 4 cases was haematological toxicity demonstrated. Toxicity has not proved to be of importance in the usual dose range. These podophyllin derivatives caused no radiopotentiation. Catalase determinations on 4 patients proved to be of value as an index of response.

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