Zilliaccus, 1963 ; Queenan and Nakamoto, 1964). On the other hand, to our knowledge nobody has yet described the transfer of F.E.s into the maternal circulation during operative termination of pregnancy at an early stage, and our survey was designed to answer this question. Our results plainly indicate that the number of F.E.s in the circulation rises significantly under these conditions. A finding of interest was that some F.E.s can be detected in the blood both of non-pregnant women and of men, though it must be pointed out that the pH of the buffer solution we used was higher than that originally described, and this may have had some influence on the number of eluted cells.

Thus erythrocytes containing foetal-type haemoglobin also contain a considerable amount of adult-type haemoglobin. In this connexion it must be remembered that in whole blood tested by the alkali-denaturation method the concentration of foetal-type haemoglobin amounts to at least 1% in normal people.

There are at least two possibilities to explain the raised F.E. count after operative termination of pregnancy. First, any mechanism that is responsible for producing and for mobilizing foetal-type haemoglobin may rapidly become activated. Secondly, foetal erythrocytes may pass from the embryo into the maternal circulation through the injured endometrial vessels. Some authors consider that the erythropoietic system of the adult is potentially capable of producing foetal-type haemoglobin as well (Zipursky *et al.*, 1962). It is also possible that the production of foetal-type haemoglobin during pregnancy might be enhanced, though this is uncertain. Nevertheless, the relatively short time that elapses between operative termination of pregnancy and the finding of F.E.s in the maternal bloodstream seems to support the second possibility rather than the first one. The finding that there was no rise in F.E.s in non-pregnant women who underwent curettage of the uterus seems to suggest that the mechanism is specific to pregnancy.

If the mechanism of sensitization is as we have postulated, it still remains to be determined to what extent this microtransfusion contributes to the sensitization of pregnant women when foetal-maternal rhesus incompatibility is present. As Levine (1944) and Wiener (1948) have pointed out, even 0.05 to

0.06 ml. of foetal blood may be sufficient to sensitize the mother, and on the basis of our findings it is likely that the amount of foetal blood entering the maternal circulation during the artificial termination of pregnancy is considerably more than this. Though more work on this matter is needed to prove our hypothesis, the possibility of maternal sensitization by artificial termination of pregnancy in rhesus incompatibility must always be borne in mind, particularly in first pregnancies.

Summary

We have shown that after surgical termination of pregnancy at 2–3 months the number of erythrocytes containing foetal-type haemoglobin in the maternal circulation is significantly raised. This suggests that termination of pregnancy may have an important immunizing role in foetal-maternal rhesus incompatibility.

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Urinary Homovanillic Acid in Pheochromocytoma

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Robinson *et al.* (1964) have suggested that the excretion of large amounts of the dopamine metabolites, homovanillic acid and 3-methoxytyramine, may indicate that a pheochromocytoma is malignant. Their suggestion was based on the finding of abnormal urinary excretion of these substances in only one out of 36 pheochromocytoma patients studied, this case also being the only malignant one in the series. Two additional cases of malignant pheochromocytoma with elevated urinary homovanillic acid have been reported (Sankoff and Sourkes, 1963 ; Ruthven and Sandler, 1964). On the other hand, an increased urinary excretion of dopamine was found some years ago by Weil-Malherbe (1956) in a presumably benign case of pheochromocytoma, and both dopamine and homovanillic acid have subsequently been found to be increased in two additional benign cases (Page and Jacoby, 1964 ; Ruthven and Sandler, 1964).

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We wish to report the results of measurements of urinary homovanillic acid in five patients with malignant and 10 with benign pheochromocytoma, studied during the past year. In

Excretion of Homovanillic Acid in Urine

Condition	Case	Age	Urinary H.V.A. (mg./24 hr.)
Malignant pheochromocytoma	1	12	5.1
	2	12	4.0
	3	12	3.1
	4	19	3.3
	5	31	10.2
Benign pheochromocytoma	1	24	3.3
	2	49	2.1
	3	53	7.0
	4	16	3.3
	5	12	5.6
	6	38	3.3
	7	55	6.1
	8	39	5.3
	9	29	6.4
	10	42	3.5
Six normal adult subjects			3.4–7.5

the malignant cases multiple metastases were verified at the time of surgery. Homovanillic acid determination was by a modified fluorometric assay (Sato, 1965). As shown in the Table, the only finding of abnormality was a slightly increased homovanillic acid in one of the malignant cases.

It may certainly be concluded that the absence of elevated homovanillic acid does not rule out the possibility of a malignant tumour. Contrariwise, the presence of an increased urinary homovanillic acid does not necessarily indicate malignancy, though available data suggest this finding may be more common in malignant than in benign cases.

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Preliminary Communications

Natulan (Procarbazine) Combined with Radiotherapy in Management of Inoperable Malignant Melanoma

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Natulan (N-isopropyl- α -(2-methylhydrazino)- p -toluamide hydrochloride) (procarbazine) is a benzyl-methyl hydrazine derivative with cytotoxic effect. It is rapidly metabolized *in vivo* with formation of the azo-compound through dehydrogenation.

The mechanism by which the cytotoxic effect is exerted has been claimed to be due to the formation of O and OH radicals. Berneis, Kofler, Bollag, Kaiser, and Langemann (1963), in their *in vitro* studies with Natulan under aerobic conditions, noticed a decrease in the viscosity of aqueous deoxyribonucleic acid solutions and explained this phenomenon by the formation of hydrogen peroxide by autoxidation. They pointed out that if Natulan is added immediately after irradiation of deoxyribonucleic acid the radiation effect is potentiated. It therefore seemed desirable to study the combined action of Natulan and ionizing radiation in patients with malignant tumours resistant to radiation therapy. Good results were obtained with this combination in treating malignant mesothelioma (Falkson and Jacobs, 1964; Falkson, de Villiers, and Falkson, 1965).

Todd (1965) reported improvement in two out of six cases of melanomatosis treated with Natulan. We have observed objective improvement in six out of ten cases of inoperable malignant melanoma treated with combined Natulan and radiotherapy (see Table).

CASE 1

A 52-year-old man presented with two satellite lesions near an operation scar over the sacrum. At the start of treatment with Natulan he had bilateral inguinal lymphadenopathy; on the left the glands measured 5 by 2 cm., and on the right 4 by 3 cm. There was also an enlarged lymph node in the right axilla. Three other distal metastases were also present—on the right leg, the left buttock, and the left posterior chest wall. He had lost 15 lb. (6.8 kg.) in weight. His general condition was good and he was able to carry out normal activities.

His first lesion had appeared 18 months previously over the sacral area. After surgery to this primary skin lesion he remained asymptomatic for more than a year.

All measurable tumour regressed after one month's treatment with Natulan; only a 1-cm. node remained palpable in the left inguinal area. The duration of remission has been 16 months.

CASE 2

A 38-year-old woman presented with an enormous pericardial effusion and cardiac tamponade. Malignant melanoma cells were found in the fluid, and a neck-gland biopsy confirmed the diagnosis of malignant melanoma. The primary site could not be determined. Other clinical findings at the start of treatment with Natulan were oedema pedis and ascites. She was very ill and bedridden.

Summary of Treatment

Case No.	Dosage of Natulan in mg.	Concomitant Radiotherapy	Lowest W.B.C./c.mm.
1	90,100 in 556 days	Telecobalt to both inguinal areas, each field 13×13 cm. Skin dose: 1,300 r in 13 days to each field	4,000
2	26,550 in 149 days	Telecobalt: anterior chest 13×13 cm., 1,500 r in 5 days. 15×15 cm. left supraclavicular and infraclavicular area, 1,000 r in 5 days. 15×15 cm. anterior chest, 1,000 r in 5 days	700
3	7,800 in 22 days	Telecobalt to abdomen, 17×17 cm., 500 r in 5 days	6,600
4	34,100 in 321 days	Telecobalt over sinus, 4×5 cm., 3,000 r in 2 weeks	2,700
5	38,350 in 282 days	Deep x-ray therapy: 1st 5 days, over lesions in front of ear, 2,000 r in 5 days. 4th month of treatment with Natulan: 7×5 cm. field over lesions right side of neck, 2,000 r in 5 days. 7th month of treatment with Natulan: 10×15 cm. field right side of head, 4,100 r in 4 weeks	2,300 3,200
6	19,400 in 262 days	None	
7	14,050 in 146 days	Telecobalt to right breast, including chest wall from sternum to mid-axillary line. 250 r/day, to a total of 4,000 r	3,200
8	12,700 in 94 days	Telecobalt: 2 opposing fields 11×9 cm. over upper mediastinum, 4,300 r in 3 weeks. At same time: 17×11 cm. field to left supraclavicular and axillary areas, 4,300 r	1,000
9	17,250 in 132 days	Deep x-ray therapy: 10×15 cm. left medial thigh, 2,000 r in 2 weeks. 3 months later: 10×10 cm. left inguinal area, 2,000 r in 2 weeks. 2.5×2.5 cm. circle left ankle, 4,800 r in 1 week	2,700
10	3,350 in 20 days	Deep x-ray therapy, 2 opposing fields 15×7 cm. over thoracic vertebra and mediastinum, 2,000 r in 2 weeks	6,900

Five days before the start of Natulan a pericardial paracentesis was done and 1,000 ml. of fluid was removed. Two days after the start of Natulan another 1,000 ml. of fluid was removed, followed 13 days later by 1,500 ml., and in 133 days by 1,500 ml. She improved sufficiently to walk about and go on holiday. The remission lasted for three months. The patient died 151 days after the beginning of treatment.

CASE 3

A 51-year-old woman had a history of local excision of a malignant melanoma from the right shoulder, which resulted in a symptom-free period of eight months. The lesion then recurred and was removed by broad excision; she was now readmitted with abdominal distension. The ascites was repeatedly tapped and bloody