Discussion

This trial showed that six weeks' treatment with cimetidine 1 g/day greatly enhanced the healing of gastric ulcers. The effect on the ulcer pain, however, was less pronounced than in the duodenal ulcer trials,[3] and there was little correlation between ulcer healing and symptomatic relief in the cimetidine group.

We used a simple anatomical definition of gastric ulcer, as all ulcers located above the pylorus were included. Prepyloric ulcers are often, like duodenal ulcers, associated with an increased gastric acid production, and cimetidine might be expected to be more effective for treating this type of ulcer than for treating corpus ulcers. This trial showed the opposite trend as regards both ulcer healing and symptomatic relief, but there were too few patients to provide conclusive results. Further studies are needed to elucidate this problem.

The random allocation of the patients to the two treatments resulted in the patients in the cimetidine group including a greater proportion of women and having a shorter average ulcer history than those in the placebo group. The possible influence of this uneven distribution of the patients on the result of the trial must be considered. A retrospective stratification showed that cimetidine had less effect in women than in men and that it had almost equal effects in patients with short and long histories. We therefore concluded that the randomisation did not bias our results in favour of cimetidine.

As in previous trials, there were no serious untoward effects of cimetidine. The unexpected symptoms noticed by some patients did not differ from those usually encountered in controlled trials and cannot be ascribed to cimetidine. One patient was withdrawn from the trial because of transient hyperbilirubinaemia, which may have been caused by the treatment.

Carbenoxolone promotes the healing of gastric ulcers, and we considered comparing cimetidine and carbenoxolone rather than cimetidine and placebo. We chose the latter design because of the frequent side effects of carbenoxolone.[8] Carbenoxolone is not registered in Denmark and therefore we did not deprive the patients in the placebo group of an effective treatment in current use. Nevertheless, comparative studies of carbenoxolone and cimetidine are needed as it cannot be taken for granted that the two drugs are equally effective in the same subgroups of patients with gastric ulcer.

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Kinetics of indium-111 labelled lymphocytes in normal subjects and patients with Hodgkin's disease

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Summary

The distribution in the body and the circulation in the blood of autologous lymphocytes labelled with indium-111 were studied in two normal subjects and two patients with Hodgkin's disease. Four hours after injection radioactivity was identified in the spleen, liver, and bone marrow. Radioactivity, followed by imaging and whole body scanning, began to appear in the lymph nodes four to 18 hours after injection, and some, though not all, lymph node groups in the body could be readily visualised. There were no differences between the normal subjects and the patients with Hodgkin's disease. The pattern of clearance of radioactivity from the blood was consistent with a normal circulation between blood and lymphoid tissues of the labelled lymphocytes.

Since indium-111 stays firmly attached to the cell, it seems an ideal label for studying lymphocyte kinetics, and the use of this technique may have further clinical applications.

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Introduction

Studies on the circulation and distribution of lymphocytes in man have been limited by lack of a suitable isotopic label. The ideal label would remain firmly attached to the cell and permit the distribution of radioactivity in the body to be detected for at least two days. Recent results using ^{111}In-oxine as a lymphocyte label[1] suggest that it may satisfy these criteria. In this preliminary study we followed the distribution of ^{111}In-labelled autologous lymphocytes in two normal subjects and two patients with early Hodgkin's disease. Our results suggest that this lymphocyte label is suitable for further clinical studies in man.

Methods

Two patients with Hodgkin's disease were studied shortly after diagnosis. After subsequent staging laparotomies one proved to have

stage IA and the other stage IIA disease. Two normal men were studied as controls. All four subjects were fully informed of the objects of the study and gave their consent.

LABELLING AND ADMINISTRATION OF CELLS

Four 20-ml aliquots of peripheral blood were drawn into 30-ml syringes containing preservative-free (5 IU/ml) heparin. 10 ml sterile normal saline was then added to each syringe. After mixing, the contents were gently layered over a 10-ml Ficoll-sodium metrizoate (Lymphoprep, Nyegaard, Oslo) gradient in four conical glass tubes and centrifuged at 450 *g* for 30 minutes.[2] The mononuclear cells were harvested from the interface, washed twice to remove plasma, and resuspended in 5 ml normal saline. The labelling technique has been described in detail elsewhere.[3]

Briefly, the ^{111}In-chelate was prepared by adding 50 μg of 8-hydroxyquinoline to a solution of carrier-free ^{111}In-Cl_3 (Radiochemical Centre, Amersham) adjusted to pH 5·5. The complex was extracted in chloroform, which was evaporated to dryness, and the residue was dissolved in 50 μl ethanol. This (200-500 μCi) was diluted to 200 μl with sterile normal saline and added dropwise to the suspended lymphocytes. These were then incubated at room temperature for 15 minutes. An equal volume of plasma was added and the suspension injected slowly into a peripheral vein. The in-vivo and in-vitro stability of cells labelled by this technique has been reported elsewhere.[1 4] The viability of the injected cells as tested by trypan blue dye exclusion exceeded 95%.

SCINTIGRAPHY AND MEASUREMENT OF RADIOACTIVITY

Scans were performed on a whole-body scanner (Ohio Nuclear Inc) at various times after the administration of labelled cells. Images were also obtained at varying intervals using a large-field gamma-camera (Toshiba 202). The proportion of injected radioactivity localised in the liver, spleen, and a small region of lumbar spine was measured from the scans.[5]

The radiation doses to which the four subjects in this series were exposed were calculated. The dose to the spleen ranged from 4 to 10 rads and that to the liver from 0·5 to 0·8 rads. The whole-body irradiation doses ranged from 0·1 to 0·3 rads.

In two subjects radioactivity was measured in blood samples taken at intervals over 48 hours. Total blood volumes were calculated from known heights and weights[6] and total blood radioactivity was expressed as a percentage of the injected dose.

Results

After the intravenous injection of labelled lymphocytes radioactivity travelled through the lung capillary bed relatively slowly. This resembled the pattern seen after the injection of labelled polymorphonuclear leucocytes.[7] Whole-body scans during the first four hours showed distribution of radioactivity in the spleen, liver, and bone marrow (see table and figs 1 and 2). After 19-26 hours distribution of radioactivity could be observed in cervical, external iliac, and inguinal lymph nodes in all subjects. In the patients with Hodgkin's disease, who received larger (400-500 μCi) doses of ^{111}In-oxine, activity could be identified in mediastinal and hilar lymph nodes also. Radioactivity was not identified in gut-associated lymphoid tissue. After 48 hours radioactivity in all the lymph nodes groups had diminished and they were less clearly defined.

The amount of radioactivity in comparable lymph node groups appeared to vary from subject to subject. Thus in one of the patients with Hodgkin's disease the migration of labelled lymphocytes into lymph nodes was more prominent than in the other patient or in the

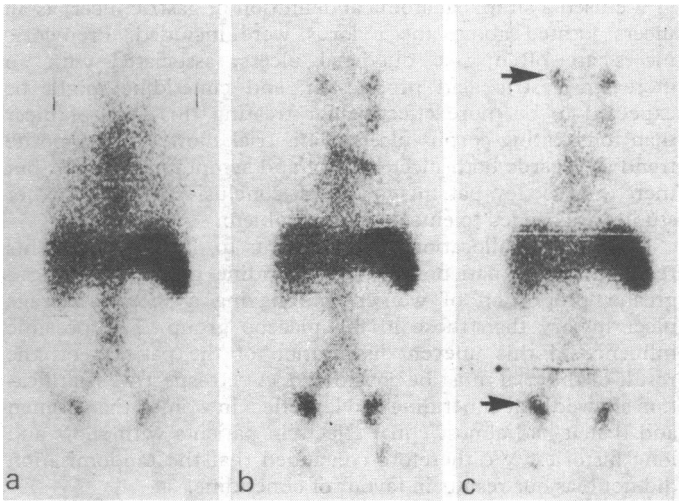

FIG 1—Case 1. Isotope scans (extending from neck to upper thigh) showing distribution of radioactivity in spleen, liver, bone marrow, and lung fields at (*a*) 2, (*b*) 18, and (*c*) 36 hours. At 36 hours lymph nodes can be identified in cervical (upper arrow), mediastinal, external iliac (lower arrow), and inguinal regions.

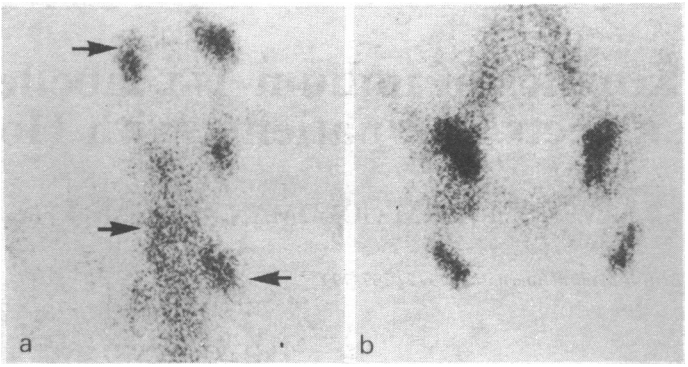

FIG 2—Case 1. Gamma-camera views of (*a*) neck and mediastinum at 18 hours. Upper arrow indicates upper cervical lymph nodes. Lower arrows indicate hilar and mediastinal lymph nodes; (*b*) pelvis at 18 hours. External iliac and inguinal lymph nodes are visible.

Percentage of total injected dose of ^{111}In-lymphocytes in spleen, liver, and a standard region of lumbar spine in four subjects at various times after administration

Case No	Dose of ^{111}In-lymphocytes (μCi)	Organ	% Dose in different organs at time after injection			
			1 h	2–4 h	19–26 h	45–46 h
1 (Hodgkin's disease)	500	Spleen	23	21	22	22
		Liver	15	10	11	11
		Spine	1·0	1·5	1·2	1·0
2 (Hodgkin's disease)	350	Spleen		26	30	31
		Liver		16	13	14
		Spine		0·9	1·2	1·1
3	250	Spleen		35	39	
		Liver		13	13	
		Spine		1·0	1·1	
4	200	Spleen	23		24	
		Liver	23		24	
		Spine	0·7		0·9	

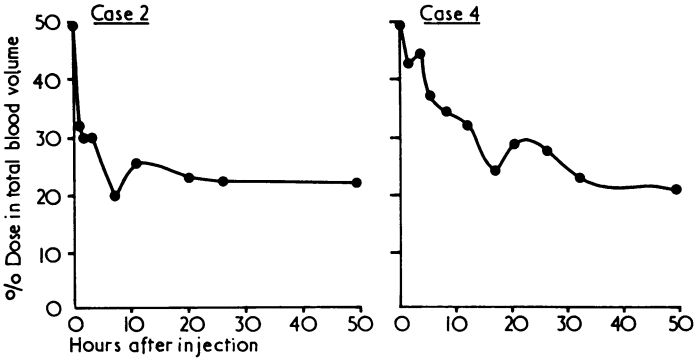

FIG 3—Fall in blood radioactivity in two subjects after transfusion of ^{111}In-labelled lymphocytes. Values are expressed as a percentage of injected dose remaining in calculated total blood volume.

normal subjects. In both patients with Hodgkin's disease localisation of radioactivity in lymph nodes thought clinically to be abnormal was neither increased nor clearly decreased in comparison with corresponding clinically normal nodes.

Clearance of radioactivity from the blood in the two subjects studied is shown in fig 3. In both cases there was an immediate loss of about half the radioactivity; radioactivity thereafter cleared more slowly down to about 25% at 12 hours. There was then a rise in activity of about 10% followed by further much slower clearance.

Discussion

^{111}In has recently been developed as a label for granulocytes, lymphocytes, and platelets.[1 8 9] With this tracer the circulation and distribution of these cells can be followed in animals and man. The label appears to be incorporated in the cell cytoplasm in a stable manner. The capacity of ^{111}In-labelled lymphocytes to recirculate normally has been shown in the rat[1]: the cells leave the blood, enter the lymphatic system, and can be recovered from the thoracic duct.

We chose to study human lymphocyte kinetics in patients with Hodgkin's disease because they are known to have abnormalities of lymphocyte function.[10] We hoped that the distribution of labelled lymphocytes might give some index of the extent of clinical disease. In fact the patients with Hodgkin's disease and the normal subjects showed similar whole-body distributions of radioactivity. In all the subjects the early distribution in the liver showed low levels comparable to those seen in the rat. This suggests that the number of non-viable labelled cells was small. In the rat about half the activity is in the spleen but this figure later falls to 30%.[1] Activity in the blood is relatively low (1-2%). Our studies showed a consistent level of splenic activity and relatively higher blood levels. Lymphocyte kinetics in rat and man need not, however, be directly comparable, and the cells labelled in this study included other mononuclear cells, especially monocytes, which do not circulate through lymphatics and might have augmented the blood pool.

Radioactivity was first identified in lymph nodes between four and 18 hours. This parallels the observations in the rat.[1] The secondary rise in peripheral blood radioactivity that occurred in between 12 and 18 hours is presumably due to re-entry of labelled lymphocytes from the thoracic duct. In the rat the transit of T cells through lymphatic tissues takes about 18 hours, while B cells take considerably longer.[11] The secondary rises we saw may therefore have been due principally to the re-entry of T cells.

Comparable groups of lymph nodes were visible in all subjects, although the proportion of labelled cells that migrated into the lymphatic tissues varied from subject to subject. Migration into lymphoid tissues seemed to be highest in one of the patients with Hodgkin's disease. In neither of the patients was there any specific localisation of radioactivity in nodes thought clinically to be abnormal. In general we noted that not all lymph-node groups were visible: in the lower part of the body we saw inguinal and external iliac but not para-aortic nodes; in the upper body we saw mediastinal and cervical nodes but not axillary, internal mammary, or supraclavicular nodes. Some of this disparity may have been due to anatomical or technical factors—for example, different relative sizes and depths of nodes—but labelled lymphocytes may migrate preferentially to lymph nodes that are immunologically "active."

This preliminary study shows that the distribution and circulation of ^{111}In-labelled autologous lymphocytes can be visualised and measured in man. The use of this technique may have further clinical applications.

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CONDENSED REPORTS

Demand for patient care

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Summary

A study was performed to determine the extent to which patients of all types were receiving inappropriate levels of care. The needs of patients in acute and supporting hospitals, people in residential homes, and patients cared for at home were assessed. A sixth of the hospital in-patients did not need hospital care, while 5% of those in residential homes and 5% of those at home did need hospital services.

These findings indicate that a realistic provision of hospital beds would be 4 per 1000 population for all specialties except regional specialties, psychiatry, mental subnormality, obstetrics, and paediatrics. About a third of these beds need to be acute, while the rest may be in supporting or community hospitals. Thus the current provision of acute beds (2·0 to 2·5 per 1000 population) exceeds actual need.

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