Middle Articles

HOSPITAL TOPICS

Pathogen-free Isolation Unit—Three Years' Experience*

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Summary: The results obtained during the first three years of a pathogen-free isolation unit containing five beds have shown that this type of unit can reduce the risk of infection in patients treated with intensive chemotherapy or in those who have granulocytopenia from various causes. It is suggested that treatment of cancer which involves these risks should be carried out routinely in sterile isolation units, and that it is urgent to build many more and much larger units.

Introduction

Intensive chemotherapy and radiotherapy in current use in the treatment of malignant disease have given some outstanding results (Mathé, 1969). Nevertheless, they can also cause periods of profound hypoplasia or aplasia of the haemopoietic and lymphopoietic systems. Thus infection has become one of the principal problems in modern cancer therapy, and is particularly formidable in malignant disease of the haemopoietic system, especially in leukaemia, where bone marrow insufficiency is often already present. In a recent study of acute leukaemia treated with intensive chemotherapy Frei *et al.* (1965) reported that bacterial infection was present in 60% of cases (of which 40% had septicaemia), while fungal infection occurred in 64% (of which 34% had septicaemia). Moreover, necropsy has confirmed that infection is the commonest cause of death in these patients.

Thus further progress in the treatment of cancer—especially of cancer of the haemopoietic system—depends on reducing the risk of infection. Hence we have set up at the Institut de Cancérologie et d'Immunogénétique a pathogen-free isolation unit (Mathé and Forestier, 1965). In this paper we describe our clinical experience in this unit over the past three years.

The Unit

Design

Fig. 1 shows that the isolation unit consists of, firstly, a series of anterooms, which ensure that the workers and their equipment gain access into the sterile "sections" only after rigorous precautions. Thus for the workers the anterooms comprise a non-sterile changing-room, a disinfection room, and a sterile changing-room. For equipment there is a sterilizing room, an autoclave, and a sterile storeroom. The suite comprises an operating-theatre, x-ray diagnosis room, rooms for the medical and nursing staff, and five single-bedded rooms for the patients. These wards open through an air-lock on to the internal corridor of the unit and also, via another air-lock, on to a

non-sterile corridor, which is irradiated for 12 hours a day by five ultraviolet lamps. If a patient becomes infected he can either be transferred from the sterile suite to another ward or be looked after via the non-sterile corridor after his room has been isolated from the remainder of the sterile unit. The patient's family can see him from the non-sterile corridor and can talk to him by using an intercom.

The incoming air is first drawn through two series of filters and then sterilized by being passed through a tunnel in which 12 large ultraviolet lamps are arranged in a circle. It is then humidified with atomized, sterile water and pumped into the unit under positive pressure at a constant temperature of 20° C. The ultraviolet lamps are installed in every room of the isolation unit and are switched on for at least 12 hours a day. An apparatus to produce an aerosol of hexylresorcinol (MacKay, 1952) giving an air concentration of 0.1 mg./cu. m. is used in each room systematically for three hours every day. Water is sterilized by ultraviolet light. In order to avoid the risk of any infection ascending from the sewers, waste water is not disposed of direct into the main drainage system but is collected into containers, which are removed (along with any other soiled material) from the air-lock leading on to the non-sterile corridor. Any equipment and food that are brought into the unit are sterilized by steam.

Bacteriological Control

Every week the medical and nursing staff, and members of the patients' families who are allowed to enter the isolation unit, have a series of bacteriological tests, samples being taken

FIG. 1.—Plan of the pathogen-free isolation unit.

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from the nose, throat, ears, skin, urine, faeces, and anus. If anybody is found to be carrying pathogenic bacteria, pathogenic fungi, or a heavy growth of a single strain of a common organism he is temporarily excluded from the unit and treated until free of the organism. Each week the air of the unit is analysed after a sample has been taken by the sedimentation technique, with Petri dishes containing trypticase soya gelatin, Chapman's medium, or Sabouraud's medium.

Swabs taken from various parts of the unit and various items of equipment are also examined for the presence of organisms. If a pathogen is discovered in one of the rooms it is then closed and the walls are cleaned with concentrated sodium hypochlorite solution, the ultraviolet lights are turned on together with the hexylresorcinol atomizer for a continuous 48-hour period.

Staff entering the isolation unit first take off their clothes in the non-sterile changing-room, wash their hands and forearms in an antiseptic bactericidal solution (hexachlorophane) for five minutes, and then put on sterile clothing in the sterile changing-room.

The patients are submitted to the same intensive bacteriological investigation as the staff before entering the unit, and this is repeated twice a week during their stay in the unit. Only those patients in whom no pathogens have been discovered are allowed to enter the unit. During their stay they receive no prophylactic antibiotic treatment—with the exception of mouthwashes containing nystatin, which are given several times a day. When clinical signs of infection are present antibiotics are used only after the results of bacteriological examinations are available, except when these signs indicate that the infection is very severe. In the latter case a combination of drugs with a very broad antibacterial spectrum is given—for example, cephalosporin together with gentamycin, or methicillin and kanamycin—subsequently this combination is changed according to the results of sensitivity tests.

Patients Nursed in the Unit

Over a period of 30 months 120 patients have been nursed in the unit, eight of whom had been admitted twice and one three times, thus comprising a total of 130 admissions. Sixty-six of the patients were males and 54 females, their ages varying between 30 months and 79 years. The average length of stay was 20 days, the minimum being 4 days and the maximum 90, and the total number of patient-days was 3,320.

Table I shows the different types of illnesses treated in the unit. The patients admitted fell into two categories: (1) those not having received any form of chemotherapy that was known to cause very severe neutropenia or those who had neutropenia before the start of treatment, and (2) those having previously received chemotherapy that had caused neutropenia. In each

TABLE I.—Patients Nursed in the Pathogen-free Isolation Unit

Disease	No. of Patients	No. of Admissions	Reason for Admission to Unit	
			Preventive (Before Chemotherapy)	Neutropenia After Chemotherapy
Acute leukaemia ..	51	60	53	7
Chronic lymphocytic leukaemia ..	1	1	—	1
Lymphoblastosarcoma ..	8	8	4	4
Hodgkin's disease ..	26	26	15	11
Reticulosarcoma ..	8	8	3	5
Myeloma ..	1	1	—	—
Polycythaemia ..	1	1	—	1
Breast cancer ..	12	12	5	7
Testicular tumours ..	3	4	4	—
Malignant melanoma ..	1	1	1	—
Gastrointestinal tumours ..	6	6	5	1
Metastasis from solid undetected primary tumours ..	1	1	—	1
Bone marrow aplasia (chloramphenicol) ..	1	1	—	1
Total ..	120	130	91	39

of the 130 courses of treatment the polymorphonuclear leucocyte count was below 1,000/cu. mm., and in 95 (73%) it was less than 500/cu. mm.

Results

Psychological Reactions

We have observed no severe psychological disturbances in any of the 120 patients admitted to the unit. Most of them were apprehensive about their admission to the unit, but tolerated their stay there perfectly well; this was also true of those patients who remained in the unit for longer than a month.

Infectious Complications

Table II indicates the types of clinical infections that have been encountered; urinary infections and septicaemia were the most frequent. In four cases of septicaemia the infection was the immediate cause of death.

TABLE II.—Types of Infections Encountered

Urinary infections ..	24
Septicaemia ..	8
Rhinopharyngeal infections ..	3
Stomatitis ..	4
Pulmonary infections ..	1
Total ..	40

There is a close relation between the incidence of infection and the number of circulating polymorphonuclear leucocytes (Table III).

TABLE III.—Relation Between Frequency of Infections and Polymorphonuclear Counts

No. of Infections	Polymorphonuclears/cu. mm.	
	< 500	> 500
40	31	9

The chief organisms isolated during these infections (Table IV) were enterobacteria (17 cases), pseudomonas (two cases), streptococci (10 cases), staphylococci (six cases), and alcaligenes (one case). Four infections were due to *Candida albicans*, predominantly a stomatitis in every case. Finally, routine

TABLE IV.—Organisms Isolated

Infections			Carriers Discovered during Course of their Admission	
<i>Escherichia coli</i> ..	9		<i>Proteus vulgaris</i> ..	2
<i>E. freundii</i> ..	2		<i>E. coli</i> ..	2
<i>Klebsiella pneumoniae</i> ..	4		<i>Staphylococcus aureus</i> ..	5
<i>Proteus vulgaris</i> ..	1		<i>K. pneumoniae</i> ..	1
<i>Proteus mirabilis</i> ..	1		<i>Ps. aeruginosa</i> ..	1
<i>Pseudomonas aeruginosa</i> ..	2			
<i>Alcaligenes faecalis</i> ..	1			
<i>Staphylococcus aureus</i> ..	6			
<i>Streptococcus faecalis</i> ..	10			
<i>Candida albicans</i> ..	4			

TABLE V.—Neutropenia and Its Associated Infections in Acute Leukaemic Patients

Reason for Admission	Polymorphonuclear Leucocytes/cu. mm.					Body Temperature above 38° C.		No. of Patients with Infections		
	No. of Admissions	< 500		> 500	Total Duration of Stay in Unit	No. of Patients	No. of Days	Mild	Severe	Lethal
		No. of Patients	No. of Days							
Preventive	53	47	689	986	1,675	27	178	13*	3	4
Post-chemotherapy	8	7	33	87	120	1	4	0	0	0

* Two of these patients had two infections.

systematic examination of 11 patients showed the presence of pathogens in the nose and mouth of six patients, and in the urine in five.

In 61 admissions for acute leukaemia (Table V) we have seen 15 mild infections, three severe infections that were controlled by treatment, and four lethal infections (septicaemia). These last seven patients were in a very advanced stage of their diseases when chemotherapy was undertaken.

In the 43 patients with lymphoma, on the other hand (Table VI), regardless of the indication for admitting the patient to the unit and despite the frequency of neutropenia no severe infection was observed. Infections in patients with solid tumours were also rare; only one severe infection was observed in 24 of the admissions (Table VII).

TABLE VI.—Neutropenia and Its Associated Infections in Patients with Lymphoma

Reason for Admission	No. of Admissions	Polymorphonuclear Leucocytes/cu. mm.			Total Duration of Stay in Unit	Body Temperature above 38° C.		No. of Patients with Infections		
		< 500		> 500 No. of Days		No. of Patients	No. of Days	Mild	Severe	Lethal
		No. of Patients	No. of Days							
Preventive Post- chemo- therapy	21	13	115	366	481	8	56	5	0	0
	22	17	193	282	475	10	55	6*	0	0

* One of whom had two infections.

TABLE VII.—Neutropenia and Its Associated Infections in Patients with Solid Tumours

Reason for Admission	No. of Admissions	Polymorphonuclear Leucocytes/cu. mm.			Total Duration of Stay in Unit	Body Temperature above 38° C.		No. of Patients with Infections		
		< 500		> 500 No. of Days		No. of Patients	No. of Days	Mild	Severe	Lethal
		No. of Patients	No. of Days							
Preventive Post- chemo- therapy	15	4	19	338	357	3	13	1	1	0
	9	7	76	53	129	4	33	3*	0	0

* One of these patients had two infections.

One patient was admitted to the unit who had presented with myeloid aplasia after treatment with chloramphenicol. She was admitted to the unit for 83 days. For the first 54 days the polymorphonuclear leucocyte count was less than 500/cu. mm. (Fig. 2). She was not given treatment with antibiotics and during this time was afebrile and no infection occurred. Thereafter recovery was uneventful.

FIG. 2.—Temperature chart and neutrophil and platelet counts of a patient who was nursed in a pathogen-free room for 12 weeks and who was not infected, though she had a severe neutropenia and thrombocytopenia.

Discussion

Theoretically the value of this kind of pathogen-free isolation unit in the prevention of infection in patients with hypoplasia or aplasia of the bone marrow could be assessed only after a random trial. In such a trial alternate patients, taken at random, would be treated either in the isolation unit or with conventional hospital treatment. Nevertheless, for obvious reasons such a trial is both impossible and unjustifiable. The patients treated in our unit were selected—this being necessary because of the limited number of beds. We have admitted to the unit those patients who had hypoplasia of the bone marrow before they were given chemotherapy and in whom there would have been a considerable risk of aplasia during such a course of treatment—and consequently of infection. In the second group we chose patients who had particularly severe bone marrow aplasia occurring after chemotherapy, this being the reason for such a large proportion of the patients having granulocyte counts of under 500/cu. mm.

We think that it is possible to compare the incidence of infection and death from infection between, on the one hand, patients treated in the unit and, on the other hand, those treated conventionally—particularly if only those patients suffering from acute leukaemia (the most homogeneous group of patients) are considered.

Table VIII shows that there is a statistically very significant difference between the incidence of infection in the two groups of patients.

TABLE VIII.—Frequency of Infection in Patients Suffering from Acute Leukaemia

	In Conventional Hospital Ward	In Unit	
All infections ..	94/117 (80%)	20/61 (33%)	$\chi^2 = 75.0$
Lethal infections ..	20/117 (17%)	4/61 (6.5%)	$\chi^2 = 3.76$

The percentage of infections in patients with acute leukaemia, treated with intensive chemotherapy under normal hospital conditions, though very high—80%—is still lower than that reported by Frei *et al.* (1965) from Bethesda. Comparisons cannot be made with other treatment centres, since the bacteriological investigations were not carried out in such a systematic fashion.

At the present time our figures for such a clinical trial form the largest series in the world and have shown the importance of this type of unit in diminishing the risk of infection that is inherent in intensive chemotherapy or after prolonged radiotherapy. It is difficult to compare the different techniques that can be used to diminish the risk of exogenous infection—particularly the relative merits of a sterile unit with those of an “isolator” system, which has been tried in the United States (Levitan and Perry, 1968). Nevertheless, our type of isolation unit has the advantage of not causing any psychological disturbances in the patients, even when their stay is as long as three months—a stay, moreover, which could be very difficult in an “isolator.”

Our results have shown that the most formidable infections which remain in a sterile unit are those due to endogenous organisms. This problem has still to be solved, for prophylactic antibiotics at present appear to be far more dangerous than they are effective (Cattan, 1966; Schneider, 1967).

Above all our results raise the question of the wider use of pathogen-free isolation units. It is now evident that all forms of effective anticancer therapy have to be intensive, and should be carried out in specially constructed isolation units and not in conventional hospital wards. In the latter the frequency of infection, which is sometimes fatal, remains high despite progress in antibiotic therapy and the use of leucocyte transfusions. These infections always interfere with vigorous antimitotic therapy and influence the overall therapeutic results (Cattan, 1966; Schwarzenberg *et al.*, 1966a, 1966b).

It is clear, moreover, that the bacteriologist is a key member of any team that wishes to treat malignant disease with maximum efficiency and the minimum of risk.

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MEDICAL EDUCATION

Clinical Haematology—Proposals by Royal College of Physicians

The Royal College of Physicians has recently published a report¹ of a Committee set up to discuss whether clinical haematology should be added to the list of specialties. The report points out that in the past few years the care of patients with disorders of the blood and blood-forming organs has increased in complexity, partly owing to the special expertise required for the application of more effective treatment and partly owing to the increased knowledge and experience required to interpret the results of laboratory tests, which have become more numerous, intricate, and precise.

Experienced Physician

Saying that it is undeniable that much of the clinical care of patients with blood diseases falls under the head of general medicine, the report goes on to state that "it is inappropriate for patients suffering from such complaints to be under the clinical care of one whose work is essentially in the laboratory. They demand the services of a general physician with the special experience and skills indicated in the first paragraph. These requirements can only be met by the training of clinical haematologists."

In the report's view the responsibility of the clinical pathologist for much of the specialized management of patients with blood diseases has never been wholly satisfactory, for this is against the universally accepted principle that one man—who should clearly be a physician, trained and experienced in the field—should have the responsibility for the bedside care of the patient.

The Committee is anxious once more to emphasize the importance of laboratory haematologists, who must continue to carry out the bulk of haematological examinations. "The physician haematologist and the medical laboratory worker are complementary, and the staff of a large general hospital should include both. Experience has already shown that such co-operation can be richly productive and rewarding."

Continuing, the Committee says that it is satisfied that in any large hospital there are more than enough patients to justify the existence of a clinical haematology department. Moreover, at the present time there are several young physicians who are eager to devote themselves to clinical haematology but can see little security in the future while the specialty is deprived of official recognition, and no appropriate posts exist.

Training Schedule

The Committee therefore unanimously recommends that clinical haematology should be recognized as a specialty. The Department of Health and Social Security should be urged to encourage the establishment of suitable posts for training. The following draft schedule of training is suggested. After the preregistration year three years should be spent in postregistration hospital posts—that is, house-physician, house-surgeon, or resident in a special hospital or in a special department of a general hospital, or laboratory posts in sciences basic to medicine, or a research post. A period as a resident clinical

pathologist would be especially useful. During this three years, the report continues, a minimum of one should be spent in a routine haematological laboratory, and one in general clinical medicine or paediatrics at registrar or equivalent level. After this a further three or four years would be spent obtaining further specialist experience of general medicine and clinical and laboratory haematology.

All appointments should be in hospitals recommended as suitable for training in clinical haematology, general medicine, or paediatrics. In general, all "university hospitals" with facilities for clinical haematology would be recommended as suitable, and arrangements are in force for making recommendations of posts in other hospitals and institutions. A year could with advantage be spent in research or other special experience at home or abroad at some stage, and no strict sequence of posts need be observed before appointment to a senior registrarship or equivalent post. Research may be pursued contemporaneously with registrar experience. Finally, time spent in general practice or working overseas or in the medical branch of one of the services might be recognized as making up part of the training.

REFERENCE

- ¹ *Report of the Committee on Clinical Haematology, 1968. Royal College of Physicians of London.* The members of the Committee were: Professor Sir MAX ROSENHEIM, P.R.C.P.; Professor L. J. WITTS; Sir RONALD BODLEY SCOTT (Chairman); Dr. M. C. G. ISRAELS; Professor J. V. DACIE, F.R.S.; Professor R. H. GIRDWOOD; Professor T. A. J. FRANKERD; Dr. M. C. BRAIN; Dr. G. H. FAIRLEY; Sir KENNETH ROBSON; and Dr. P. A. EMERSON.

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