gradings. This difference between the control groups was probably related to general ill health since patients requiring operation for gastrointestinal disease tend to be more ill than patients with benign breast disease. Obviously, misleading results may be obtained if normal patients are used as controls for some malignancies.

Can this depression of cellular immune response be related to prognosis? While the prognosis of malignancy is clearly related to the outcome of the interplay of host and tumour little is known of the basic factors involved in this interaction. The idea that general immune competence plays a part would be supported if the changes in immune competence in different tumours corresponded to the outcome seen in that type. Broadly speaking, prognosis is similar for breast and colonic tumours of equivalent stage but very much worse for gastric cancer. The depression of cellular immunity in gastric cancer, however, consistently lay between that seen for breast (least depression) and colonic (greatest depression) cancers. Thus, depression of cellular immune competence alone cannot explain the different prognoses of gastric and colonic cancer. The possibility that on the tumour side of the equation the different sites are so disparate as to mask the effects of immune competence is not excluded; but the stage-related findings in breast cancer were also against general immune competence playing an important part in determining or reflecting prognosis, though only prolonged prospective follow-up can give an answer in relation to individual cases of early cancer. The differences between breast and gastrointestinal cancers were unlikely to be related to sex differences since normal men consistently have a better response to the Mantoux test.⁸

Some workers^{9, 10} have suggested that depression of cellular immunity is stage related though the data are not extensive. Our figures showed an insignificant tendency in this direction in colonic cancer. In the patients with breast cancer it is difficult to assess the significance of variations between the different stages. Clearly, neither total volume of tumour nor the presence of lymph node metastases was closely related to immune depression either in the breast or gastrointestinal cases. There is no clear explanation for the curious findings in the breast cancer patients. It would be tempting to suggest that some of the small tumours with a poor response had occult metastases and so really belonged to stage D; the corresponding argument to explain the good response of the large tumours would be that a good immune response had facilitated control of dissemination

but had been unable to prevent continued local growth of the primary tumour. Follow-up of these patients, however, showed that the prognosis of the patients with a large local tumour and lymph node metastases (stage C₂) was extremely poor in spite of the well maintained cellular immunity. The difference between small and large tumours is so clearcut that it cannot be ignored, and it seems that these differences must reflect some facets of the biological processes in the host tumour interrelationship that are not understood.

The considerably depressed responses in gastrointestinal cancer might suggest a nutritional effect. Nutritional factors and general "illness" undoubtedly play some part (as seen in the different control groups) but if they were the only factors involved the most profound depression would be expected to occur in gastric rather than colonic cancer. Depressed immunity seems to result from a summation of at least two effects—nutritional factors and some specific effect of the tumour itself. The view that the latter may be the more important of the two would be supported by the finding that cellular immunity returns to normal after curative surgery. But though this sometimes occurs it is by no means invariably seen.

Thus, the changes in cellular immunity in cancer are complex and vary between different tumours. It would be easy to dismiss them as random and of little importance but they probably point to the fact that the host tumour interaction is more complex than is commonly believed. Greater study of general immunity and careful correlation with clinical and prognostic factors may well throw much light on the role of immunity in cancer.

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SHORT REPORTS

Five-year Follow-up of Jamaican Adults with Sickle Cell Anaemia

In 1968 we reported the clinical and haematological features of 60 Jamaican patients over 30 years old with homozygous sickle cell (S.S.) disease.¹ Though reports from other countries²⁻⁵ confirm that some patients with S.S. disease may survive into their fifth, sixth, and even

seventh decades, little is known about their mortality. In 1973 we performed a 5-year follow-up on our 60 patients (original case numbers in parentheses).

Results

Two patients (42 and 50) were subsequently classified as sickle- β thalassaemia, on the basis of raised Hb A₂ levels and family studies and have been excluded. Five patients were untraced, one (35) was last seen in good health

Actual and Expected Deaths* of 53 Jamaicans with S.S. Haemoglobin after Five Years

Age at Initial Examination	Males			Females			Both Sexes		
	No.	Actual Deaths	Expected Deaths	No.	Actual Deaths	Expected Deaths	No.	Actual Deaths	Expected Deaths
30-34	11	—	0.163	13	1	0.180	24	1	0.343
34-39	9	2	0.161	8	2	0.146	17	4	0.307
40-44	1	2	0.029	2	2	0.047	3	4	0.076
45-49	0	—	0.000	2	1	0.061	2	1	0.061
50-54	3	1	0.196	3	—	0.148	6	1	0.344
55-59	1	—	0.093	0	—	0.000	1	—	0.093
Total	25	5	0.642	28	6	0.582	53	11	1.224

*Based on Jamaica Life Tables, 1959-61.

in July 1971, another (48) has not been seen since October 1967, and three (8, 13, and 24) had emigrated in good health in 1968, 1969, and 1971, respectively. Eleven patients had died. The table shows the actual number of deaths compared with the expected number in 5-year age groups. Cerebrovascular disease probably caused death in four cases, and cardiovascular disease in two. Two others died suddenly and unexpectedly while recovering from a severe painful crisis and the lack of causal pathology at necropsy was compatible with a cardiac arrhythmia. Forty two were traced during 1973, of whom 32 had regularly attended the clinic during the past five years, six had been specially contacted and examined for the present survey, and four (2, 22, 40, and 54) had not been seen but had corresponded or were reliably reported alive. Thirty three patients were in reasonable health, 22 of them in full time employment. In nine cases, symptoms of the disease interfered with normal activity, owing to leg ulceration in six, low haemoglobin levels in two, hepatic enlargement and abdominal swelling in one.

When analysed in 5-year age groups the haematological characteristics of the elderly group did not differ significantly from those of younger ages.

Discussion

Prolonged survival in S.S. disease does not mean a benign process. In only two patients was it diagnosed incidentally and these admitted to mild symptoms on direct questioning. Most patients had experienced typical and occasionally severe symptoms of S.S. disease when younger. After the age of 30, painful crises tended to become less frequent and less severe, leg ulcers healed, and aplastic crises were less common. Despite this symptomatic amelioration, however, vessel obstruction and ischaemia progressed. Occlusion of the peripheral retinal vessels resulting in retinitis proliferans occurred in 7/20 (35%) of patients aged over 48 compared with 1/30 (3%) of those under this age. Abnormalities of renal function also increase with age.

There is now good evidence that S.S. disease is compatible with survival into the fourth, fifth, and sixth decades though increased mortality, characteristic at younger ages, persists. There is a lower proportion of elderly patients attending the clinic than would be expected had the condition been benign. This might result from either a high mortality or from the lack of diagnosis in the elderly. Our evidence confirms the high mortality, which was eleven times that expected in the general Jamaican population. Late presentation is also a contributing factor, however, since 57 patients over the age of 30 including 10 over 50 have joined the clinic during the 5-year follow-up.

It is not understood why some patients survive to comparatively old ages and others die young. The role of other genetic and environmental factors⁵ remains speculative. So also does the natural history of the disease. A prospective study from birth is the only way of obtaining an accurate assessment of the natural history of the disease and would also allow the influence of environmental and genetic factors to be assessed.

I wish to thank Dr. Michael Ashcroft of the M.R.C. Epidemiology Unit for the calculations of expected deaths in the Jamaican population.

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Method of Using Pressurized Aerosols

The efficacy of inhaled bronchodilators depends on demonstrating the correct method to the patient. The timing of the inhalations is important when the inhaler is taken according to the manufacturer's instructions. The inhaler appears to be far more effective if the aerosol is released at some distance from the open mouth rather than directly into it—for two reasons: firstly, a larger fraction of the dose from the aerosol would be impacted on the back of the palate when the aerosol was discharged at a close range (that is, closed mouth); and, secondly, better entraining of the aerosol with the inspired air

parallel to but wider than the aerosol jet. A single blind method was used to test this hypothesis in terms of improving the patient's peak expiratory flow rates (PEFR) and preliminary results confirm this.

Materials and Methods

Thirty one patients with airway obstruction, which was reversible by at least 10%, inhaled isoprenaline. Most patients were familiar with using inhaled bronchodilators. The peak flow rate was measured by the standard Wright peak flow meter. Isoprenaline was delivered by two puffs of the standard Medihaler Iso, which contained 0.1 mg of isoprenaline. Patients were instructed to use the inhaler at a distance of 40 mm from the open mouth with a blank (open mouth). Their technique with the orthodox (closed mouth) was also confirmed. They were randomly allocated to two groups and their response to isoprenaline inhaler was followed according to the protocol below:

	GROUP A	GROUP B
	Control PFR	Control PFR
Time 0 min.	Inhale with open mouth	Inhale with closed mouth
5 "	PEFR	PEFR
10 "	Inhale with closed mouth	Inhale with open mouth
15 "	PEFR	PEFR

Three patients attended one week later, when they were put in the opposite group. A doctor allocated the patients to treatment groups and instructed them. Peak flow readings were recorded by a technician, who was unaware of the patient's group. The initial peak flow was best of three readings and subsequent peak flows the better of two readings. Readings were converted to percentages of the control PEFR (see table).

Peak Flow Rates in Patients Inhaling with Open (A) and Closed (B) Mouth

Group	Control Peak Flow		Initial Improvement		Further Improvement	
	Range	Mean	Range	Mean	Range	Mean
A	60-400	195	7-78	30.2	-9-+23	3.9
B	70-420	212	-2-+40	14.5	-1-+29	10.1

Groups A and B had the same mean peak flow measurement before treatment. The mean percentage initial improvement in PEFR was significantly higher in Group A with mouth open than in Group B with mouth closed ($t=2.83$; $P<0.05$). The mean percentage further improvement in Group B with mouth open was also significantly greater than in Group A with mouth closed ($t=2.21$; $P<0.05$). The overall improvement in PEFR after both treatments (open + closed mouth) did not differ significantly between A and B ($P>0.05$).

Discussion

With the Medihaler, as used in these experiments, impaction judged by wetting sheets of paper no longer occurs at approximately 11 cm. The delivery of the standard salbutamol (Ventolin) and steroid inhalers (Bextosol and Becotide) appear to be more powerful. The impaction distance is up to 22 cm with Ventolin and rather less with the steroid preparations. In all cases this distance is far longer than the distance from the mouthpiece to the soft palate when using the closed mouth method. That most of the aerosol is not entrained is confirmed by the fact that most of the dose is swallowed.¹⁻³ The distribution of thrush (the most common complication with steroid inhalers) on the soft palate suggests that impaction is an important factor. Moreover, limited personal experience suggests that if the open mouth method is used thrush is less persistent with high doses of steroid inhaler, and the lesions are smaller and more widely distributed in the mouth, presumably because of less impaction on the soft palate.

I wish to thank Mr. R. A. McNay, statistician, Northern Regional Health Authority, for performing the statistical analysis.

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