is needed if rational measures are to be implemented in the community to reduce the high prevalence.

The long term morbidity of diabetes in British Asians is unknown. Observations on over 400 Asian and 490 European diabetic patients attending Ealing Hospital suggest that the prevalence of retinopathy and symptomatic ischaemic heart disease is similar in the two groups. In view of the earlier age of presentation in Asians and the clear relation between the duration of diabetes and the development of complications we might envisage a considerable morbidity from retinal, renal, neurological, and arterial disease over the next few decades.

The results of this survey are important in planning services for diabetic patients in health districts with large Asian communities. There are over one million Asians in Britain, and their age distribution is similar to that in Southall. As more young Asians reach middle age an appreciable increase in the number diagnosed as diabetic may be expected. More Asian speaking dietitians and more educational aids for Asian patients with diabetes are needed. Research should be directed towards defining possible environmental factors, evaluating preventive measures, and protecting this at risk population from the complications of the disease.

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Postmarketing surveillance of the safety of cimetidine: mortality during second, third, and fourth years of follow up

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Abstract

A previous report analysed the pattern of mortality during the first year of follow up among 9928 patients taking cimetidine who were recruited to a postmarketing drug surveillance study in Glasgow, Nottingham, Oxford, and Portsmouth. A further analysis has now been conducted extending the period of follow up to four years.

The 12 month report noted that cimetidine was being given, knowingly or unknowingly, in the late stages of

many diseases and also to counter the adverse gastric effects of other drugs used in the treatment of serious disorders. This finding was underlined by a steady fall in the excess death rate among cimetidine users with increasing length of follow up, such that by the fourth year the pattern of observed deaths was not much different from that expected on the basis of national rates.

Some excess of observed over expected deaths from gastric cancer, lung cancer, and urinary disorders was still apparent after four years of follow up, but there was no evidence that cimetidine was responsible. Indeed, no fatal disorder emerged as being associated with cimetidine during the follow up period. Deaths from the complications of disease related to gastric acid occurred in only 38 of the 9928 subjects over the four years.

These findings provide further evidence of the safety of cimetidine.

Introduction

The methods used in our study of the safety of cimetidine have been described in detail in an interim report on gastric cancer¹ and in reports on mortality² and morbidity³ during the first year of follow up. In brief, four centres (Glasgow, Nottingham, Oxford, and Portsmouth) took part in the investigation and a

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total of 9928 takers of cimetidine were identified between 1977 and 1979 by means of copies of prescriptions supplied either by the Prescription Pricing Bureau (Nottingham) or by local pharmacists (the three other centres). The takers' medical records were traced at each practice and various items of information (including occurrence of major morbidity and death) noted at a follow up visit about 15 months later. Controls (who did not take cimetidine) were also identified but are not considered in this report.

TABLE I—Observed deaths (O) from all causes and observed deaths divided by deaths expected (O/E) at national rates* in each centre in each study year

Centre		Study year			
		1	2	3	4
Glasgow	{ O	59	40	44	31
	{ O/E	1.4	1.2	1.3	0.9
Nottingham	{ O	65	53	43	46
	{ O/E	1.6	1.5	1.2	1.3
Oxford	{ O	123	81	56	52
	{ O/E	2.0	1.5	1.0	1.0
Portsmouth	{ O	138	76	76	66
	{ O/E	2.2	1.4	1.4	1.2
Total	{ O	385	250	219	195
	{ O/E	1.9	1.4	1.2	1.1

*Expected deaths for year 1 (based on national rates for 1979) taken from Colin-Jones *et al* (1983).² Expected deaths for years 2-4 based on national rates for 1981. Calculations made for each sex separately within five year age groupings.

TABLE II—Observed and expected numbers of deaths for individual ICD chapters

ICD chapter	Study year				Expected deaths in each year†
	1	2	3	4	
001-139 Infectious and parasitic diseases	1	0	2	1	0.6
140-239 Neoplasms	152	75	47	56	41.4*
240-279 Endocrine, nutritional, metabolic, and immunity diseases	3	1	4	1	1.9
280-289 Blood and blood forming disorders	0	1	2	0	0.4
290-319 Mental disorders	1	1	0	0	1.0
320-389 Diseases of nervous system and sense organs	0	1	7	3	2.0
390-459 Diseases of circulatory system	131	112	93	79	90.8
460-519 Diseases of respiratory system	40	21	31	24	26.3
520-579 Diseases of digestive system	33	21	20	11	5.0*
580-629 Diseases of genitourinary system	8	6	8	10	2.4**
680-709 Diseases of skin and subcutaneous tissue	0	0	0	1	0.2
710-739 Diseases of musculoskeletal system etc	2	2	1	3	0.9
740-759 Congenital anomalies	0	1	0	0	0.2
800-999 Injury and poisoning	14	8	4	6	4.9
Total	385	250	219	195	178.0

Fourth year deaths *v* expected deaths: **p* < 0.05; ***p* < 0.01.
†Calculated for third year of study (see text and table I).

We decided that it would be valuable to monitor over a long period mortality among takers of cimetidine who had survived the first year, partly to see if the unexpectedly high death rates which had been noted in certain disease categories were maintained, and partly to see if any new trends in mortality emerged. This paper summarises our findings to the end of the fourth year of follow up.

Present study

METHODS

The Office of Population Censuses and Surveys agreed to flag our cohort of cimetidine takers in the NHS Central Registries at Southport and Edinburgh. Copies of death certificates identifying the underlying cause of death were then sent to the monitoring centre (Oxford), usually within six months of death. Each centre retrieved the relevant medical records for each taker who had died and noted brief details about the terminal illness, use of cimetidine after the initial study year, and any important errors in the certification of the underlying cause of death. As we were no longer receiving notifications of prescriptions for cimetidine, and as the information in the medical records was likely to be incomplete, we recorded only a rough indication of cimetidine use during each quarter of each year.

Mortality was examined according to sex, underlying cause of death, study year, and centre. Expected numbers of deaths for the second to fourth years of follow up were calculated using Office of Population Censuses and Surveys mortality statistics for England and Wales for 1981. Initially we computed expected deaths for each study year separately; the variation in the numbers obtained from year to year was very small, however, so the figures presented here are based on those calculated for the third year of follow up.

We also divided takers who were alive at the start of the second study year into three groups according to the amount of cimetidine they had taken during the first study year. Light users were defined as those who had taken up to 199 tablets (of 200 mg each), medium users as those who had taken 200-599 tablets, and heavy users as those who had taken 600 tablets or more. The pattern of mortality in these three groups was then examined during the succeeding three years.

To obtain some information about the extent to which takers continued to use cimetidine beyond the survey year we identified a 10% sample of those who were still alive in 1984 and contacted their general practitioners. The questions which we asked were deliberately kept simple: we inquired merely about the prescription of cimetidine and ranitidine (and certain other drugs) during each quarter of 1984. We did not ask about the quantities prescribed or about dosage.

SUBJECTS

Of the 9928 takers who entered the study, 375 were known to have died during the first year of follow up at the time that we prepared our first mortality report.² Accordingly, the identifying particulars of

9553 subjects were sent to the NHS Central Registries. Of these subjects, 9377 (98.2%; 5890 men, mean age 50 years; 3487 women, mean age 56 years) were successfully identified and flagged. The remaining 176 takers (who were untraced in the registries or had gone overseas) were omitted from subsequent analyses.

Results

PATTERN OF MORTALITY IN COMPLETE COHORT

The NHS Central Registries identified 10 deaths among subjects previously lost to follow up, yielding a revised first year total of 385 deaths.

Table I shows the overall pattern of mortality in the four study centres, both separately and in combination, during the four years of follow up. There was considerable variation in mortality among the centres during the first survey year, presumably reflecting differences in the types of patient receiving cimetidine. Nevertheless, the ratios of observed to expected deaths declined steadily over the period, closely approaching unity in the fourth year.

Table II gives the observed and expected numbers of deaths during the four study years for each of the main chapters of the International Classification of Diseases (ICD; 9th revision). Again, differences between observed and expected numbers were generally small by the fourth study year, although the excesses of deaths from

neoplasms (56 observed *v* 41.4 expected), digestive diseases (11 observed *v* 5.0 expected), and genitourinary diseases (10 observed *v* 2.4 expected) were statistically significant.

Within the chapter headings underlying causes of death were examined according to the detailed classification presented in our earlier report.² Results are given here only for certain individual diseases which required special attention, either because there were major differences between taker and control mortality in the first study year or because they were particularly important causes of death. In none of the disease categories omitted from the tables were the data a cause for concern. Furthermore, in addition to the analysis by underlying cause of death, the principal investigators in each centre examined other diagnoses appearing on the death certificate—for example, in part II—to determine whether any disorders which might be drug related had been missed—for example, blood dyscrasias, liver disorders, renal damage, skin disorders. In the event this exercise added nothing to our analysis of the underlying causes of death.

Table III gives details about observed and expected deaths for the selected diseases. As before, differences between observed deaths and expected deaths were in general much greater in the first year of the study than in the fourth year. Even in the fourth year, however, there was some excess mortality from gastric cancer, lung cancer, non-malignant diseases of the oesophagus, stomach, and duodenum, and diseases of the urinary system.

Diseases of oesophagus, stomach, and duodenum and gastrointestinal haemorrhage

Twenty six deaths occurring during years 2, 3, and 4 of the study were attributed to diseases of the oesophagus, stomach, and duodenum and gastrointestinal haemorrhage. No information about cimetidine use could be obtained for one patient who died from a gastrointestinal haemorrhage. Thirteen patients had no record of cimetidine use within six months of their terminal event, which comprised perforation in nine patients (gastric ulcer in two, duodenal ulcer in four, peptic ulcer in three) and haemorrhage in four patients (gastric ulcer in one, duodenal ulcer in two, peptic ulcer in one). In addition, two patients had no record of cimetidine use within three months and seven weeks respectively of their deaths from perforated gastric ulcers.

Seven patients were taking cimetidine at the time of their terminal illness. Three of these were taking 1 g daily: a 92 year old woman with an ulcerated oesophageal stricture, an 80 year old woman who was treated for gastrointestinal bleeding secondary to analgesic abuse and who succumbed to further bleeding 22 days later, and an 82 year old man with senile dementia whose perforated duodenal ulcer was treated conservatively for one month before he died. A 76 year old woman was taking 600-800 mg cimetidine daily when she died from a gastric ulcer haemorrhage, and two men aged 75 and 79 with alcoholic cirrhosis were both taking 400 mg daily when they suffered a gastric ulcer haemorrhage and a duodenal ulcer haemorrhage respectively. Lastly, a 53 year old man suffering from diabetes mellitus and severe psoriatic arthropathy had been taking 1 g cimetidine daily for two years for a duodenal ulcer and drug induced dyspepsia. The dose was reduced to 400 mg daily, and 25 days later he was admitted to hospital with abdominal pain and melaena. He died after surgery for a bleeding duodenal ulcer.

Three patients died soon after stopping taking the drug. A 69 year old man severely ill with chronic obstructive airways disease and cardiac failure had been taking 1 g cimetidine daily, probably on an irregular basis. He was admitted to hospital with a suspected myocardial infarction and the cimetidine was stopped. He died suddenly

12 days later, and necropsy showed a duodenal ulcer haemorrhage and carcinoma of the bronchus. A 77 year old man had been taking 600-800 mg daily until he underwent an emergency appendicectomy. He died eight days later from a massive gastric ulcer haemorrhage. Finally, an 86 year old woman with stomal ulceration had her regular daily dose of 600-800 mg discontinued when she was terminally ill after a stroke. She died five days later from a gastric ulcer haemorrhage.

Gastric cancer

Of the 26 patients who died from cancer of the stomach during years 2-4 of the study, in three the diagnosis was made before cimetidine was started and in a fourth the diagnosis was based on clinical evidence alone. All the remaining 22 patients presented with advanced cancer. About half were known to have had a history of gastric or duodenal ulceration when cimetidine was started, but in most there was no evidence other than clinical that the ulcer was active at that time. The mean interval between first exposure to cimetidine and diagnosis was 19.7 months (range 2-45 months). We could not assess the amount of cimetidine taken by four patients, but in the 18 others the mean number of 200 mg tablets prescribed was 690 (range 210-1500).

Cancer of trachea, bronchus, and lung

Of the 64 patients who were certified as having died from lung cancer during years 2-4 of the study, we have information on 56. Six were diagnosed before cimetidine was started and 26 had stopped taking the drug at least 12 months before the cancer was discovered, although many of these had received several courses of treatment. In addition, two patients were wrongly certified as having died from lung cancer; one had an asbestos related mesothelioma and the other laryngeal cancer. Thus 22 patients were diagnosed while taking the drug or within one year of stopping it. The duration of treatment varied from a few weeks to several years. Of the 64 subjects who died, 35 were aged over 65 years and 45 were recorded as having smoked, though others may have done so.

Diseases of the urinary system

There were 23 deaths from diseases of the urinary system in years 2-4 of the study in the following age groups: 30-39 (one case), 50-59 (one), 60-69 (four), 70-79 (five), 80-89 (10), 90 or more (two). Twelve of the deaths were attributed to renal failure, 10 to pyelonephritis or other urinary tract infection, and one to renal calculus. We have no information about cimetidine use for four patients, whose ages at death were 78, 81, 85, and 86 years. In 14 patients the disorder was established before starting cimetidine or was an obvious consequence of other disease. Two patients had stopped the drug nine and 30 months respectively before entering terminal renal failure. The remaining three patients were aged 81, 88, and 90 years, and in no case did the history contain anything of note.

PATTERN OF MORTALITY AND AMOUNT OF CIMETIDINE USED

Table IV shows observed and expected numbers of deaths in years 2, 3, and 4 of the study in relation to the amount of cimetidine taken

TABLE III—Observed and expected numbers of deaths for selected ICD rubrics

ICD rubric	Study year				Expected deaths in each year†
	1	2	3	4	
150-0-150-9 Malignant neoplasm oesophagus	7	1	3	2	1.3
151-0-151-9 Malignant neoplasm stomach	45	12	6	8	3.5*
153-0-154-1 Malignant neoplasm colon and rectum	15	11	7	2	5.2
162-0-162-9 Malignant neoplasm trachea, bronchus, lung	35	25	17	22	12.5*
174-0-174-9 Malignant neoplasm female breast	5	5	0	4	3.0
200-0-208-9 Lymphomas, myelomas, leukaemias	15	9	2	3	2.3
410-0-414-9 Ischaemic heart disease	81	61	59	46	51.5
430-438 Cerebrovascular disease	14	25	19	14	20.8
530-537, 578 Diseases of oesophagus, stomach, and duodenum and gastrointestinal haemorrhage	12	12	10	4	1.8
571 Chronic liver disease and cirrhosis	13	6	4	1	0.7
580-599 Urinary system diseases	7	5	8	10	2.1*

Fourth year deaths *v* expected deaths: **p* < 0.05.

†Calculated for third year of study (see text and table I).

TABLE IV—Observed (O) and expected (E) numbers of deaths in second, third, and fourth years of study in relation to amount of cimetidine taken during first year of study (200 mg tablets)

Cause of death		Cimetidine intake in first year		
		Light (≤199 tablets)	Medium (200-599 tablets)	Heavy (≥600 tablets)
Gastrointestinal causes				
Malignant neoplasm of stomach (ICD 151.0-151.9)	{ O	4	9	13
	{ E	7.8	8.6	9.6
	{ O/E	0.51	1.05	1.35
Diseases of oesophagus, stomach, and duodenum and gastrointestinal haemorrhage (ICD 530-537, 578)	{ O	6	9	11
	{ E	8.2	8.7	9.1
	{ O/E	0.73	1.03	1.21
Remaining gastrointestinal diseases (including neoplasms)	{ O	18	15	28
	{ E	19.0	20.1	21.9
	{ O/E	0.95	0.75	1.28
Total	{ O	28	33	52
	{ E	35.0	37.4	40.6
	{ O/E	0.80	0.88	1.28
Non-gastrointestinal causes				
Malignant neoplasm of trachea, bronchus, and lung (ICD 162.0-162.9)	{ O	21	21	22
	{ E	22.0	20.4	21.6
	{ O/E	0.95	1.03	1.02
Urinary system diseases (ICD 580-599)	{ O	7	2	14
	{ E	6.7	7.4	8.9
	{ O/E	1.04	0.27	1.57
Remaining non-gastrointestinal causes (including neoplasms)	{ O	137	110	217
	{ E	138.2	147.3	178.5
	{ O/E	0.99	0.75	1.22
Total	{ O	165	133	253
	{ E	166.9	175.1	209.0
	{ O/E	0.99	0.76	1.21

Expected numbers of deaths in this table calculated internally by indirect standardisation (see text).

during the first year. The expected numbers were calculated internally by indirect standardisation within strata defined by sex, age (five year groupings), and centre. Accordingly, in table IV the sum of the observed deaths within any diagnostic group is equal to the sum of the expected deaths.

The overall results are given separately for gastrointestinal and non-gastrointestinal causes of death, while, in addition, detailed data are provided for the individual diseases or disease groups mentioned above. Although the ratio of observed to expected deaths was highest in the "heavy" dosage group for each of the diagnostic categories (save for lung cancer), the ratios showed a clear trend with dose only for gastric cancer and diseases of the oesophagus, stomach, and duodenum and gastrointestinal haemorrhage—disorders which present with symptoms such as dyspepsia which would stimulate recurrent prescriptions for cimetidine.

In view of the fact that a raised mortality ratio was seen in the heavy dosage group for "remaining non-gastrointestinal causes" we undertook a detailed analysis of individual groups of causes of death to see if the excess was concentrated in any particular category. This was found not to be the case (results not given).

USE OF H₂ RECEPTOR ANTAGONISTS IN 1984

Adequate replies about the prescription of H₂ receptor antagonists were obtained from general practitioners for 77% of the patients about whom we inquired. Of these patients, 36% were prescribed cimetidine or ranitidine at least once during 1984, while 15% received such a prescription in all quarters of the year. Dividing the data according to whether the patients concerned were in the light, medium, or heavy dosage groups during the survey year showed that the proportions receiving any prescription and the proportions receiving a prescription in all quarters of 1984 were 22% and 7%, 37% and 9%, and 49% and 25%, respectively. Thus the categorisation of the patients according to their level of drug usage during the survey year was still reflected by prescribing patterns in 1984. Of the patients receiving an H₂ receptor antagonist in 1984, 81% received only cimetidine, 14% only ranitidine, and 5% both drugs.

Discussion

In our 12 month mortality report² we noted that cimetidine was being given, knowingly or unknowingly, in the late stages of many diseases and also to counter the adverse gastric effects of other drugs used in the treatment of serious disorders. This

finding is underlined by the steady fall in the excess death rate among users of cimetidine with increasing length of follow up, such that by the fourth year the pattern of observed deaths was not much different from that expected on the basis of national mortality figures.

Deaths from the complications of disease related to gastric acid (which made up most of the fatalities coded to ICD rubrics 530-537 and 578 in our analysis) occurred at an increased rate throughout follow up. It should be noted, however, that only 38 subjects out of the 9928 originally recruited died from these causes during the four years. Furthermore, most of those who died were very old and many were suffering from other serious conditions which contributed to their demise. We have been unable to identify any suitable series of patients with acid related disease from the "pre-cimetidine era" with which to compare our series, but we suggest that the extremely low mortality rate which we have observed may reflect a beneficial effect of cimetidine.

The excess of observed over expected deaths from gastric cancer in years 3 and 4 of the study was modest. Furthermore, it is now known that in many patients with gastric cancer there is a prolonged period during which the tumour remains localised to the mucosa before becoming invasive. Tsukuma *et al* observed that the five year survival rate in 34 patients with early gastric cancer who had not undergone surgical resection was 64.5%.⁴ If the Japanese experience can be applied to our patients, then an excess of gastric cancer might be expected for several years after the administration of cimetidine (or any other drug relieving dyspepsia) if the drug was inappropriately prescribed. The association between dosage of cimetidine and mortality from gastric cancer observed in our series (table IV) has many possible explanations apart from a causal one. For example, patients with unrecognised gastric cancer may well have had particularly intractable symptoms resulting in prolonged cimetidine treatment. Gastric cancer is to be the subject of a detailed report.

The continuing high death rate from lung cancer is somewhat puzzling. It must, presumably, reflect the smoking habits of the cimetidine takers (which were not recorded). The absence of any association between the amount of cimetidine taken during the first study year and subsequent mortality from lung cancer argues against any possible relation between the drug and the disease.

The excess of deaths from diseases of the urinary system among cimetidine takers was also unexpected. In contrast with the other associations, this one showed no tendency to diminish with time. Cimetidine tends to cause a slight rise in plasma creatinine concentration early in treatment,⁵ presumably by interfering with tubular function, but we did not record any instance where this effect was considered to be relevant. Indeed, examination of the individual case histories disclosed an elderly group of patients suffering from a multiplicity of disorders, many of which were present before cimetidine was started. It is difficult to prove or disprove whether a drug is influencing an established irreversible process, but in our view it is extremely unlikely that cimetidine played any part in the demise of the few patients who may have been taking the drug in the terminal stages of their illness.

A clear trend towards an increased mortality ratio with dose of cimetidine prescribed during the survey year (which was reflected in the pattern of prescribing during 1984) was seen only with gastric cancer and acid related disease, where such trends were to be expected, and we are reassured by the fact that no fatal disorder emerged as being associated with cimetidine during the follow up period. Rather, as already emphasised, the trend was for associations seen during the first year of follow up to diminish with time.

In conclusion, we believe that our data further support the view that cimetidine is a safe drug. We intend to continue to

monitor the pattern of mortality to ensure that no unexpected trends emerge.

We thank Mr T Lucas, who organised and monitored the study and conducted the fieldwork in Oxfordshire; Mrs M Edmond and Mrs S Wood, who conducted the fieldwork in Nottingham and Portsmouth, respectively; Mr J Beresford, who managed the computing; and Mrs D Collinge, who provided secretarial services. Dr A Flind gave help and advice. We also thank the many general practitioners in the four areas for their continued support. NHS Central Registry, family practitioner committee, and hospital records staff have also given invaluable cooperation.

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Thirty four year follow up of patients with breast cancer in clinical trial of postoperative radiotherapy

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Abstract

An extended follow up to a maximum of 34 years was carried out on a series of 1461 patients who had been entered into a randomised clinical trial comparing immediate postoperative radiotherapy (treated group) with an optional delayed radiotherapy policy (watched group) after Halsted radical mastectomy for operable breast cancer. Long term survival was compared separately in patients with negative and positive axillary nodes and in two periods when different techniques of radiotherapy were used.

No significant differences were noted in survival overall or in any subgroup. In patients with negative axillary nodes treated in the earlier period when the "quadrate" radiotherapy technique was used, however, the difference in survival was of borderline significance ($p=0.052$), to the benefit of the watched group. Because of the large numbers of patients entered and the long follow up any possible harmful or beneficial effect of immediate postoperative radiotherapy would have been apparent in the results of this trial. The absence of any such effect implies that postoperative radiotherapy given to prevent or delay local recurrence of breast cancer is unlikely to be associated with a detectable effect on survival.

Introduction

The propensity of metastases to develop many years after treatment for breast cancer is well known. It is important, therefore, in comparing the effects of various modalities of treatment, particularly for early breast cancer, to assess the long term results. Benefits associated with one particular treatment in the short or medium term may not be sustained in the long term; equally, harmful sequels may become apparent only much later. To change policies of treatment based on premature analyses of early trends may be prejudicial to patients in the long term.

Other studies have shown survival to 20 or more years after treatment for early carcinoma of the breast,¹⁻⁴ but these were not randomised clinical trials. We are able to present the results of an extended follow up to a maximum of 34 years in a group of 1461 patients who were entered into one of the first recorded randomised clinical trials.

Patients and methods

From January 1949 to June 1955 a total of 1461 patients with operable carcinoma of the breast were entered into a clinical trial carried out at this hospital. Patients with operable (stage I and II) carcinoma of the breast had Halsted radical mastectomy. They were then randomised to have either immediate postoperative radiotherapy (treated group) or delayed radiotherapy, when treatment was carried out only if the patient developed local recurrence (watched group). In the first part of the trial, up to June 1952, patients assigned to the treated group received radiotherapy by the "quadrate" technique to the axilla and operative flaps. From July 1952 to June 1955 a "peripheral" technique was used, in which only the axilla, supraclavicular region, and parasternal area were treated. Patients underwent close physical follow up at this hospital for five years after entry to the trial. If well the patient was dismissed and subsequent follow up arranged by

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