the lung . . . through crushing forces which collapse part of the lung . . . may act as a trip hammer to set off the train of events leading ultimately to the invasion of the interstitial tissues of the body by air from the lungs."

Apart from my series, only 12 cases of ventilator-induced pneumoperitoneum have been recorded in adults. The present cases were collected over three years at one hospital, two being seen in the last six months. The syndrome is unlikely to be an isolated occurrence and is probably more common than reports suggest. Awareness of artificial ventilation as a cause of pneumoperitoneum will reduce the number of needless laparotomies performed on patients who are already seriously ill.

I thank Mr D B Clarke for advice and help in managing cases 1 and 4; Mr P S London for encouragement and permission to report cases 1, 2, and 4; Mr N Tubbs for referring case 3; and Mr E Leary for invaluable advice on all matters.

References

1 Gantt, C, Daniel, W W, and Hallenbeck, G A, *American Journal of Surgery*, 1977, **134,** 411.
2 Wolloch, Y, Dintsman, M, and Weiss, A, *Archives of Surgery*, 1972, **105,** 723.
3 Lozman, H, and Newman, A J, *American Journal of Obstetrics and Gynecology*, 1956, **72,** 903.
4 Glauser, F, and Bartlett, R H, *Chest*, 1974, **66,** 536.
5 Stringfield, J T, *et al*, *Journal of the American Medical Association*, 1976, **235,** 744.
6 Turner, W W, and William, J F, *Archives of Surgery*, 1977, **112,** 723.
7 Krausz, M, and Manny, J, *Journal of Trauma*, 1977, **17,** 238.
8 Joannides, M, and Tsoulos, G D, *Archives of Surgery*, 1930, **21,** 333.
9 Macklin, C G, *Archives of Internal Medicine*, 1939, **64,** 913.
10 Macklin, M T, and Macklin, C C, *Medicine*, 1944, **23,** 281.
11 Grosfield, J L, Boger, D, and Clatworthy, H W, *Journal of Pediatric Surgery*, 1971, **6,** 339.

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Unknown primary adenocarcinoma: incidence of overinvestigation and natural history

J F STEWART, M H N TATTERSALL, R L WOODS, R M FOX

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Summary and conclusions

Out of 1300 patients referred to a medical oncology unit, there were 87 with metastatic cancer in whom a primary tumour site was not evident from the history and after physical examination and chest radiography had been carried out. An analysis of the investigations performed in these patients and their results showed that in only eight of the 87 patients did non-surgical investigations at presentation determine the primary site. In two patients it was identified by diagnostic laparotomy, and in a further 13 clinical follow-up led to recognition of the primary tumour site before death.

Few investigations should be performed in patients in whom the primary site is not known since they have a low yield, and in our population identifying the primary tumour did not improve the outcome or alter management. Treatable tumours should be excluded, and this may be done in most cases by simple blood tests, particularly those measuring acid phosphatase activity and other tumour markers.

Introduction

Patients often present with metastatic malignant disease without an obvious primary tumour. The dilemma facing the clinician is how aggressively to try to identify the primary site. Traditionally, in medical wards large series of non-invasive investigations are undertaken, while in surgical wards a more rapid progression to exploratory laparotomy is common. The argument for pursuing the primary site aggressively in these patients is usually based on two beliefs: that finding the primary site might, firstly, lead to specific antitumour treatment and, secondly, give a better guide to prognosis. A possible further reason may be the diagnostic challenge posed by such patients.

We have reviewed the clinical histories of 1300 patients with malignant disease referred to this newly established medical oncology department in a major teaching hospital. Patients who presented initially with metastatic adenocarcinoma and undifferentiated carcinoma (confirmed histologically or cytologically) in whom the clinical history, full physical examination including breast palpation and pelvic examination, and chest radiography did not identify the primary site were studied. Eighty-seven patients (6·7%) fell into this category, and the investigations in these patients and natural history of the disease constitute this report.

Patients and methods

The clinical staff of this institute saw 1300 patients with cancer between January 1977 and October 1978. All clinical histories were reviewed retrospectively, and patients who presented initially with metastatic cancer without a documented primary site on clinical history, examination, and chest radiography were studied further. Only patients with metastatic non-squamous carcinoma based on review of the initial histological specimens were included. All investigations were recorded, including those before referral and those that were not designed specifically to identify the primary tumour site. The unit's policy was to discourage exhaustive investigations to find the primary site, but in patients considered to be suitable for trials of chemotherapy staging investigations to assess the disease were encouraged. The radiological procedures were routine, and nuclear-medicine scans were performed in a single department where the bone-scanning radionucleide used is technetium-labelled pyrophosphate and the liver-scanning agent technetium-99m sulphacolloid. Technetium pertechnetate was used for thyroid and brain scans, and cerebral CAT scans were performed in certain patients. The haematological and biochemical investigations were by standard techniques.

The results of investigations designed to identify the primary sites

Sydney Cancer Therapy Unit, Ludwig Institute for Cancer Research, Royal Prince Alfred Hospital, Sydney, Australia
J F STEWART, MB, BS, registrar
M H N TATTERSALL, FRACP, director, professor of cancer medicine
R L WOODS, MRCP, assistant physician
R M FOX, FRACP, associate professor of cancer medicine

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TABLE I—*Age distribution of all patients referred with cancer and of patients with unknown primary adenocarcinomas. Figures are numbers (%) of patients*

Age (years):	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90
Total population referred		33 (2·5)	65 (5)	103 (8)	233 (18)	377 (29)	313 (24)	143 (11)	33 (2·5)
Patients with unknown primary adenocarcinomas		1 (1)	2 (2·5)	8 (9)	17 (19)	18 (21)	27 (31)	14 (16·5)	

TABLE II—*Numbers of patients having physical signs at various sites, and numbers of patients in whom each site was the predominant one*

Site	No showing clinical signs at site	No in which site predominant
Skin	7	1
Bone	23	5
Lymph nodes	25	13
Liver	30	15
Other abdominal sites	25	16
Lungs:		
Parenchyma	24	15*
Pleura	27	7
Central nervous system	7	7
Local mass	7	4
Miscellaneous:		
Pericardial effusion	1	1
Cushing's syndrome	1	1
Obstruction of superior vena cava	1	1
Lymphoedema	1	1

*Seen only on radiography in eight cases.

TABLE III—*Site of tissue analysed initially by biopsy and cytologically. (Figures in parentheses indicate number of open surgical procedures at these sites)*

Site	No of patients
Biopsy	
Lymph node	21
Liver	14 (6)
Lung or pleura	11 (6)
Abdominal mass (not liver)	8
Local mass	5
Skin	4
Bone marrow	4
Bone	4
Epidural site	2
Total	73*
Cytological examination	
Pleural	12
Ascitic	4
Aspiration	2
Total	18*

*In four cases the diagnosis was established by biopsy and cytological examination.

were classified as false-positive or true-positive according to the findings at operation or postmortem examination. The survival of patients was measured from the time of the initial histological diagnosis of malignant disease.

Results

Altogether, 45 male and 42 female patients were eligible for inclusion in the analysis. Table I shows the ages of the patients studied and of the total population seen at this institute during the period of analysis. The patients with unknown primary adenocarcinoma tended to be slightly older than the general population of patients with cancer.

Physical signs at presentation—Table II shows the clinical signs and predominant sites of disease at initial presentation. In eight patients the abnormality was seen only on chest radiography. The initial diagnosis of malignant disease was established by open biopsy in 69 patients, by cytology in 14, and by both methods in four. Table III shows the sites of tissue analysed initially.

Diagnostic investigations—Many investigations were carried out to identify the site of the primary tumour. The primary site was identified before death in 23 patients (26%), in only 10 (11%) by investigations (including laparotomy) conducted at the time of initial presentation.

Blood tests—Serum acid phosphatase activity was measured in only 22 of the 45 male patients and was raised in three. In two patients prostatic cancer was diagnosed by biopsy, but in the third patient no histological evidence of prostatic carcinoma was obtained. Concentrations of β-human chorionic gonadotrophin (β-HCG) were raised in the two patients subsequently shown to have germ-cell tumours. Serum concentrations of carcinoembryonic antigen (CEA) were measured in 25 of the 87 patients: they were appreciably raised in eight patients and marginally raised in seven. In four of the eight patients with appreciably increased concentrations (>25 ng/ml) a primary tumour site was diagnosed before death: two had colonic primary tumours, one a lung carcinoma, and one an ovarian adenocarcinoma. A diagnosis was made before death in two of the 17 with normal or marginally raised concentrations: one had ovarian and the other a thyroid carcinoma.

Radiological investigations—Intravenous pyelograms (IVPs) were obtained in 35 patients and in two were thought to be diagnostic of primary renal tumours. These were both false-positive results, since subsequent investigations did not confirm a primary tumour at this site. The IVP showed a false-negative result in one patient, who presented 12 months later with haematuria and at operation was found to have a primary renal carcinoma. Fourteen of the 42 female patients underwent mammography, which in no case was diagnostic of primary breast cancer.

Barium studies—Twenty-four barium-meal examinations were performed, and four were thought to be diagnostic of gastric carcinoma. One patient had a primary gastric tumour, but in the other three the results were false-positive, since subsequent investigations did not confirm primary gastric tumours. One false-negative result was obtained, in a patient who at postmortem examination was found to have a primary gastric tumour. Twenty-seven barium enemas were performed, and in seven cases were thought to be diagnostic of primary colorectal neoplasms. Four of these patients proved to have primary colorectal tumours, but in the remaining three subsequent investigations failed to confirm such tumours.

Radionucleide scans—One of the 16 thyroid scans was thought to be diagnostic of a primary carcinoma, but this was a false-positive result since subsequent investigation did not confirm a thyroid cancer. One false-negative thyroid scan was obtained in a patient who one year later was found to have a primary follicular carcinoma of the thyroid.

TABLE IV—*Relation between metastatic appearances on liver scans and results of liver function tests*

Results of liver function tests*	No of scans showing secondary liver tumours	No of scans with normal or non-specific appearances
Normal	3	10
1 Abnormal	5	12
2 Abnormal	10	5
⩾3 Abnormal	5	1
Total	23	31†

*Tests included measurement of bilirubin and albumin concentrations and of activities of alkaline phosphatase, γ-glutamyl transpeptidase or lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase.
†In three patients with normal scans liver function tests were not performed.

Endoscopy—Sigmoidoscopy was performed in 13 patients and was diagnostic in one; biopsy confirmed the diagnosis. One of the 17 bronchoscopies was diagnostic of a primary neoplasm, which was subsequently confirmed at postmortem examination. Three patients had extrinsic compression of the bronchial tree consistent with pulmonary metastases. Gastroscopy was performed in seven patients and no tumours were seen. There were no false-negative results.

Staging investigations—Many investigations designed to establish the extent of tumour dissemination were carried out in the 87 patients. Twenty-three out of 54 scans of the liver and spleen suggested metastatic disease. Table IV shows the relation between biochemical evidence of altered liver function and liver-scan abnormalities. Table

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V shows the relation between palpable hepatomegaly and scan appearance. In patients with palpable hepatomegaly and substantially altered liver function 12 liver scans were diagnostic of metastatic disease and only one was normal. Bone scans were obtained in 22 patients: in 11 the appearances were abnormal and consistent with metastatic bone disease. Nine of the patients with abnormal bone scans had bone pain, while three with similar symptoms had normal scans. Results of haematological tests were abnormal in 31 patients.

TABLE V—*Relation between metastatic appearances on liver scan and clinical hepatomegaly*

Liver-scan appearance	Liver palpable	Liver impalpable
Consistent with secondaries	18	5
Normal or non-specific	4	27
Total	22	32

Fourteen had severe anaemia (haemoglobin $<11{\cdot}5$ g/dl) and 14 neutrophil leucocytosis (neutrophil count $>10\times10^9$/l (10 000/mm^3)). Only two patients had severe anaemia and leucocytosis. Three patients had leucoerythroblastic anaemia and one pronounced eosinophilia. There was no clear relation between the existence of anaemia and a primary gastrointestinal tumour. Four patients had thrombocytopenia ($<125\times10^9$/l) and 12 thrombocytosis ($>525\times10^9$/l).

Brain scans—Ten patients underwent CAT scanning. The scans were abnormal in six, but only two were consistent with metastatic brain disease. The other abnormalities included features suggestive of cerebral infarction, meningioma (incidental), and benign cortical atrophy.

Overall result of investigations designed to find primary tumour site—In only 23 patients (26%) was the primary tumour site identified during life. In eight patients non-invasive investigations identified the primary tumour, and in a further two (one with gastric and one with pancreatic cancer) laparotomy established the diagnosis. In the remaining patients follow-up, often over several months, led to the identification of the primary tumour site by the development of new symptoms. Table VI shows the primary sites in the 23 cases.

TABLE VI—*Primary sites identified during life*

Site	No of patients	No diagnosed by initial, non-invasive investigations
Colon	4	4
Ovary	4	0
Lung	3	1
Kidney	2	0
Stomach	2*	1
Prostate	2	2
Germ cell	2	0
Pancreas	1*	0
Thyroid	2	0
Hepatoma	1	0
Total	23	8

*One of each primary site detected by laparotomy.

Results of postmortem examination—Twelve patients are still alive. Thirty-five of the remaining 75 died in hospital, and postmortem examinations were performed in 16 of these. Table VII shows the results of the postmortem examinations and of histological examination of any tissue removed at that time. In four of the 16 patients a diagnosis of the primary site had been made during life, which in each case was confirmed. In three patients the results of histological examination of tissue removed after death combined with those of the initial histological examination led to a change in the diagnosis from adenocarcinoma to melanoma (one), Hodgkin's disease (one), and histiocytic lymphoma (one). In two patients the postmortem examination failed to disclose the primary tumour. In the remaining seven patients in whom the primary site had not been identified during life postmortem examination showed that four patients had primary lung cancers, one each a stomach and colon cancer, and one a primary hepatoma.

Survival—Twelve patients are known to be alive and 12 are lost to follow-up. Figure 1 shows the survival curve of patients known to have died or to be alive. The median survival from histological diagnosis was 13-14 weeks. One patient was still alive 112 weeks after the initial presentation and diagnosis. The patients were divided according to the predominant site of metastatic disease—namely, lymphadenopathy or pulmonary or liver disease. Figure 2 shows the survival curves for these three different patient groups. Patients who presented with lymphadenopathy had a prolonged median survival compared with the other two groups. There was no difference in median survival time between patients in whom the primary tumour site was identified during life and those in whom it was not (fig 3). The duration of symptoms before histological diagnosis did not affect survival.

Age—Patients under the mean age (57 years) had a median survival of 20 weeks compared with nine weeks for those who were older. In two patients death was not directly related to malignant disease, as one died after an open lung biopsy and one of a saddle embolus four weeks after histological diagnosis of intra-abdominal tumour.

TABLE VII—*Results of postmortem examinations*

Outcome	No of patients
Confirmation of primary tumour diagnosed during life	4
Diagnosis changed after tissue examination*	3
No primary tumour found	2
Primary tumour found in:	
Lung	4
Stomach	1
Colon	1
Hepatoma	1
Total No of postmortem examinations	16

*Histological examination showed melanoma (one case), Hodgkin's disease (one), and histiocytic lymphoma (one).

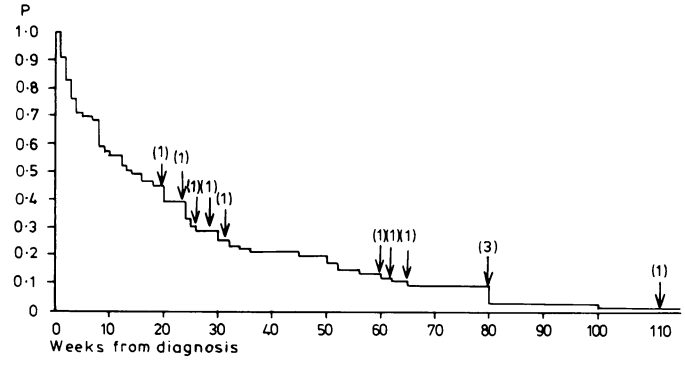

FIG 1—Overall survival from diagnosis of 75 patients with unknown primary cancer known to have died or to be still alive. Figures in parentheses refer to living patients.

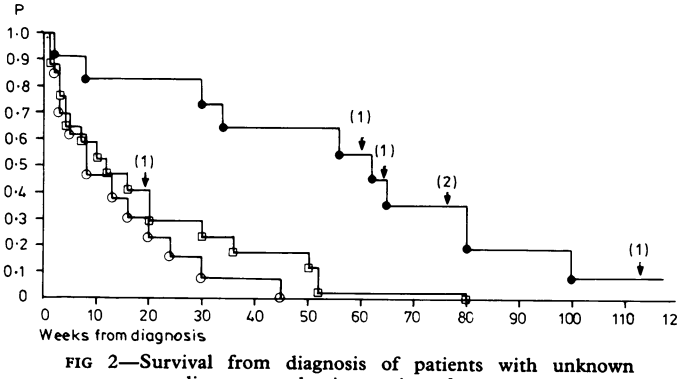

FIG 2—Survival from diagnosis of patients with unknown cancer according to predominant site of metastatic disease. Figures in parentheses refer to living patients.
●=Patients with lymphadenopathy (11; two lost to follow-up). □=Patients with pulmonary disease (17; five lost to follow-up). ○=Patients with liver disease (13; two lost to follow-up).

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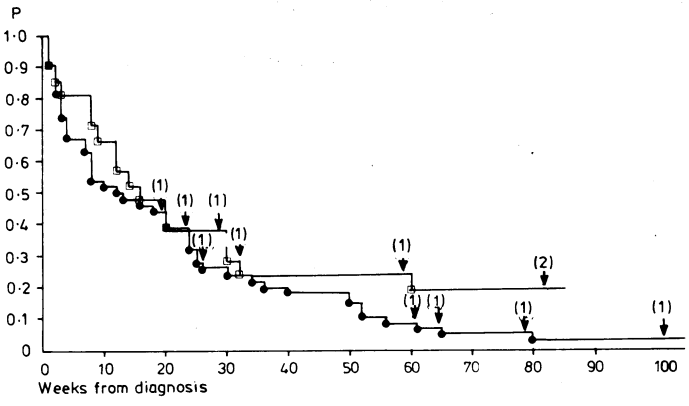

FIG 3—Survival from diagnosis of patients with unknown primary cancer according to whether or not primary cancer site was found during life.
●=Primary site not found during life. ○=Primary site found.

Discussion

Unknown primary metastatic adenocarcinoma was diagnosed in 6·7% of the patients seen at our clinic. This incidence is higher than that reported previously,[1 2] but others have restricted this diagnosis to patients in whom extensive investigations aimed at identifying the primary site have yielded negative results. We believe that the term unknown primary adenocarcinoma should include all patients who present with histologically confirmed metastatic adenocarcinoma in whom the history, clinical examination, and chest radiography do not identify the primary site.

The mean age of 57 years in our series is similar to that reported by others.[2 3] The extremely poor yield of the extensive investigations conducted in our patients (only eight primary tumour sites identified in the 87 patients) was disappointing but agrees with results reported by Osteen *et al.*[4] Many of these investigations are hard to justify in view of their poor yield and cost in time, money, and patient discomfort, particularly since they do not appear to influence the outcome. Moreover, apart from four ovarian cancers, two germ-cell tumours, and two prostatic cancers, none of the other tumours was particularly responsive to presently available systemic treatment. Thus we think that efforts should be directed at excluding the possibility of a treatable primary tumour, and this may be done by a few simple investigations—that is, measurement of acid phosphatase activity, assessment of biochemical markers of germ-cell tumours (β-HCG and α-fetoprotein), and imaging of pelvic organs. The possibility that investigations of biopsy specimens might identify sensitive tumours has been raised by reports of unknown primary tumours containing oestrogen receptors responding to hormonal treatment.[5 6] We now measure oestrogen-receptor concentrations in tumours other than breast and uterine cancers but did so in only one of the patients in this series, in whom they were absent.

The better prognosis of patients with metastatic lymphadenopathy without a primary tumour site has been reported.[3] Whether this improved survival reflects less-extensive disease rather than an immunologically mediated phenomenon is not clear. Many of the patients in our series underwent staging investigations. The purpose of these investigations may be questioned, and in general their justification is that they are baseline measurements of tumours before treatment. Analysis of our results indicated that liver scans are rarely positive in patients without severely altered liver function and hepatomegaly.

Others have reported that the commonest primary sites in patients with metastatic malignant disease and no primary tumour after investigation are the lung and pancreas.[7] The commonest sites of primary tumours in our patients were the lung, colon, and ovary. This difference presumably reflects the fact that our patient group was defined as having metastatic malignant disease with no primary tumour site at presentation before investigation. The histological diagnosis was changed after death in three of our patients, two of whom had drug-sensitive tumours. Clearly, histology should be reviewed in patients with unknown primary cancers, since those with lymphoma and germ-cell tumours in particular may have a substantially better prognosis if treated appropriately.

We are most grateful to the physicians, radiotherapists, and surgeons for referring the patients included in this analysis, and to Miss Cheryl Frewin for help in the analysis.

References

1 Holmes, F F, and Fouts, T L, *Cancer*, 1970, **26**, 916.
2 Didolkar, M S, *et al*, *Annals of Surgery*, 1977, **186**, 625.
3 Moertel, C G, *et al*, *Cancer*, 1972, **30**, 1469.
4 Osteen, R T, Kopf, G, and Wilson, R E, *American Journal of Surgery*, 1978, **135**, 494.
5 Golomb, H M, and Thomsen, S, *Archives of Internal Medicine*, 1975, **135**, 942.
6 Kiang, D T, and Kennedy, B J, *Journal of the American Medical Association*, 1977, **238**, 32.
7 Nystrom, J S, *et al*, *Seminars in Oncology*, 1977, **4**, 53.

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ONE HUNDRED YEARS AGO The supplement to the *Gazette of India* of December 14th, 1878, contains some very interesting facts as to the mortality from snake-bites, and the attempts which have been made to lessen this by promoting the destruction of poisonous snakes. From this official document we take the following statistics. In 1877, 16 777 persons were killed by snake-bites, as compared with 15 946 in the preceding year. In Madras, the mortality equalled 23 per million of the population; in Bombay, 50 per million; in Bengal, 142 per million; in the north-western provinces and Oudh, 92 per million; in the Punjab, 32 per million. On the other side of the account, we find that the number of snakes destroyed was, in 1877, 127 295, against 212 371 in 1876. The total amount paid for the destruction of snakes and wild animals was, in 1877, 103 107 rupees; in 1876, 124 574 rupees. With one exception, the local government authorities are disposed to think that the system of rewards for the destruction of snakes has not had, and probably will not have, any material effect upon the mortality. The reasons given for this distrust are interesting. It appears that a large proportion of the snakes killed were caught and brought in by professional snake-catchers from places remote from human habitations, where they would probably never have had the opportunity of killing a single human being. A careful investigation of the numerous cases of death from snake-bites shows that the majority of them occur in or near dwelling-houses. The fact that the number of females who die from snake-bites is larger than the number of males, seems to show that the cases occur in villages and homesteads rather than in the open fields. An observation by Sir Ashley Eden suggests the same conclusion. He points out that, whereas tigers kill twenty times as many cattle as they do persons, snakes kill twenty times as many persons as they do cattle. The Indian Government is of opinion that "the mortality from snake-bites is attributable to the mode of life of the people. It is preventable by them if they are prepared to change this mode of life; but it is preventable in no other way. So long as the people allow their homes to be surrounded by rank vegetation, old bricks, and rubbish, and go out into this natural abode of snakes in the night without a light, and often without any protection for their feet, so long will they be exposed to the risk of snake-bites. The recklessness of the people in regard to the adoption of ordinary precautions against accidents of this kind is so much a part of the national character, that nothing that Government can do is likely materially to effect any substantial good." It is, nevertheless, determined to continue the system of rewards, with precautions against its abuse, for some little time longer; and, at the same time, to impress upon all landed proprietors and farmers the necessity of removing from the dwellings of themselves and their labourers the arrangements for promoting the multiplication of snakes which at present surround them. (*British Medical Journal*, 1879.)

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