

## ORIGINAL ARTICLE

# Lipoprotein (a) does not participate in the early acute phase response to training or extreme physical activity and is unlikely to enhance any associated immediate cardiovascular risk

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**Aims:** To investigate the proposal that lipoprotein (a) (Lp(a)) contributes to the acute phase response and thus possibly to the acute cardiac risks associated with major physical effort.

**Methods/Results:** Fit, healthy, British army recruits were reviewed at the beginning and the end of a 10 week programme of basic training concluding with an intense 48 hour military exercise. Final recruit assessment was staggered over the last week of training, giving rise to six recruit groups, with determination of Lp(a), C reactive protein (CRP), fibrinogen, albumin, and total creatine kinase values from 12 hours to five days after the final exercise. A clear acute phase response was seen following the final exercise, marked by a significant increase in circulating concentrations of fibrinogen and a reduction of albumin, and a trend with non-significant increases in CRP.

**Conclusion:** Lp(a) did not behave as an early marker of the acute response. Previous reports may have been confounded by concurrent disease in older subjects and by late sampling. Lp(a) determination for cardiovascular risk profiling is not confounded by associated physical effort. It is also unlikely that the acute risks of major physical effort are enhanced by any process involving Lp(a).

The association of lipoprotein (a) (Lp(a)) concentrations with cardiovascular risk may arise through prothrombotic and/or atherosclerotic properties.<sup>1,2</sup> Circulating values are mainly under genetic control and closely related to isoform patterns and the number of kringle 4 type II repeats, for which the homology with plasminogen may lead to some inhibitory effects on clot lysis through competitive binding.<sup>1,3</sup> Binding to this or other ligands may also directly promote the accumulation of Lp(a) in developing atherosclerotic lesions.<sup>1</sup> The effects of a sedentary or athletic lifestyle and related factors, including exercise and diet, have also been investigated as a means of reducing Lp(a) values,<sup>4-7</sup> with conflicting reports from mostly small group studies on the status of Lp(a) as an acute phase protein.

The acute phase response (APR) is a specific, immune based reaction to several non-specific stimuli including bacterial infection, tissue damage, surgery, and strenuous physical activity. The APR includes fever, endocrine changes, alterations in immune function, leucocytosis, and increased synthesis by the liver of some proteins, the acute phase proteins, which include C reactive protein (CRP), fibrinogen, serum amyloid A,  $\alpha_1$  antrypsin, and interleukin 6.<sup>8</sup> Lp(a) has also been described as an acute phase protein, with a reported increase in response to a variety of acute stimuli including postoperative trauma,<sup>9</sup> myocardial infarction, and angina,<sup>10-12</sup> but not in rheumatoid arthritis<sup>13</sup> or during acute infection.<sup>14</sup> Min *et al* also proposed that any APR-Lp(a) response might be influenced by the apolipoprotein (a) (apo(a)) kringle 4 dependent phenotype present.<sup>15</sup> Thus, the involvement of Lp(a) in the APR is not clear cut, both in the extent and the latency of the response, notably after acute cardiac episodes,<sup>10-12</sup> and could also depend on the exact stimulus involved. Considering lifestyle, epidemiological studies have suggested that increased leisure time activity is inversely associated with serum concentrations of Lp(a),<sup>16</sup> and some preliminary studies have indicated that values may increase in

association with acute physical stress, again perhaps as a component of the APR. Fibrinogen is an acute phase protein; both fibrinogen and Lp(a) are associated with the degree of cardiovascular risk, and increased concentrations of plasma fibrinogen and Lp(a) have been coupled in some, but not all, studies of mostly older patients with symptomatic cardiovascular disease.<sup>17,18</sup> Given these associations, any event such as inflammation or injury where both fibrinogen and Lp(a) increase rapidly could enhance cardiovascular risk, including stroke,<sup>19</sup> at least in the short term and be implicated in the exercise related risk of sudden death, perhaps through contributing to the documented adverse prothrombotic shift that occurs during and shortly after extreme exercise.<sup>20</sup>

"The acute phase response is a specific, immune based reaction to several non-specific stimuli including bacterial infection, tissue damage, surgery, and strenuous physical activity"

The interpretation of laboratory data and assessment of cardiovascular risk could also be compromised by overt or undeclared major exertion before sample collection. The third report of the US national cholesterol education program adult treatment program<sup>21</sup> notes that information on Lp(a) values should be considered in the management of individual cardiovascular risk. We have studied acute phase responses to extreme exercise and relations with Lp(a) through observations on army infantry recruits taken early and late in a 10

**Abbreviations:** apo(a), apolipoprotein (a); APR, acute phase response; BMI, body mass index; CK, creatine kinase; CRP, C reactive protein; Lp(a), lipoprotein (a); ME, military exercise; NS, not significant; SDS, standard deviation

week programme of basic training, which also included a final arduous two day military exercise (ME). We are interested in the APR as a means of advancing our understanding of the physiological mechanisms involved in interindividual and intra-individual variation and the control of circulating concentrations of Lp(a), and of potential approaches to therapeutic intervention. We are also interested in the possible involvement of Lp(a) values and their variation in the exercise enhanced risk of cardiac events.

## MATERIALS AND METHODS

### Recruit selection and training protocol

With the approval of the army medical ethical committee, consecutive groups of new British Army male recruits undergoing 10 weeks of intensive training with the Army Training Regiment at Bassingbourn were selected for our study. The protocol has been described previously.<sup>22</sup> Informed written consent was obtained from all the recruits along with information regarding height, weight, medical, drug, and smoking history. All of the young men were free from disease, physically fit, and had passed the army medical examination. The training regimen includes five weeks of general fitness training and five weeks of more exhaustive prolonged physical activity. There were 69 sessions of 40 minutes duration specifically dedicated to physical training, with much of the remaining time also involving physical activity.

As part of the final assessment, the recruits were put through a strenuous ME during the ninth week of training. The ME comprised prolonged moderate physical exertion in full battledress, covering approximately 10 miles, and lasting up to 48 hours. Pretraining blood samples were taken during the first week of recruit induction. The post training blood samples (with some dropouts) were taken over the last five days of training, after the recruits had completed the ME.

The constraints of the training timetable meant that the recruits were sampled at different time points after the ME for the final assessment. Each group is shown below along with the maximum number of test results available for each recruit group.

Group 1: 12 hours post ME (n = 41)

Group 2: 24 hours post ME (n = 13)

Group 3: 48 hours post ME (n = 34)

Group 4: three days post ME (n = 19)

Group 5: four days post ME (n = 39)

Group 6: five days post ME (n = 65)

### Blood collection, transportation, and storage

Pre and post ME blood samples were obtained from each recruit group after five minutes of supine rest. Serum samples were collected into 5.5 ml Monovet gel tubes (Sarstedt Ltd, Leicester, UK), whereas the plasma samples were taken into tubes containing 3.8% trisodium citrate. All blood samples were transported on ice by car from the military training centre at Bassingbourn to our laboratory. On arrival in the laboratory, the serum gel tubes were centrifuged (1000 ×g for 10 minutes at 4°C), and the isolated serum was stored at 4°C before analysis of albumin and total creatine kinase (CK). An aliquot of serum for Lp(a) and CRP measurements was frozen and stored at -70°C until our study was completed. Citrated plasma samples were centrifuged (300 ×g for 15 minutes at 4°C) on arrival and the platelet poor plasma was collected and stored at -20°C until the end of our study. All of the assays reported here are carried out in CPA accredited laboratories and are supported by external quality assurance schemes.

### Lp(a) assay

Paired serum samples (before and after the ME) from each recruit were thawed at 37°C and assayed together. The Lp(a)

**Table 1** Baseline values for demographic variables at intake (mean/SD)

Intake results	Mean	SD
Age (years)	18.8	0.11
Height (cm)	175.4	0.5
Weight (kg)	67.9	0.6
BMI (kg/m <sup>2</sup> )	22.2	0.12
Initial blood pressure (mm Hg)	119/72	0.85/0.74
Final blood pressure (mm Hg)	120/70	0.84/0.85
Smokers/non-smokers (n)	150/131	

Blood pressure readings were obtained before and after five minutes of supine rest. There were no significant differences between groups for any of the variables measured.  
BMI, body mass index.

**Table 2** Baseline data at intake categorised by C reactive protein (CRP) concentration as low and high groups (<5/>5g/l)

	Low CRP (<5g/l)		High CRP (>5g/l)	
	CRP	Lp(a)	CRP	Lp(a)
N	84	78	63	78
Median	3.6	0.11	6.3	0.09
Range	1-4.8	0-1.05	0-41.5	0-1.0

There was no significant difference between Lp(a) values for the low and high CRP groups (Mann Whitney U test, p=0.80).

concentration was determined using an enzyme linked immunosorbent assay based method supplied by Immuno Ltd, Dunton Green, Kent, UK.<sup>23</sup> The assay used a monospecific antihuman apo(a) antibody coupled with peroxidase. To improve the range of the Lp(a) assay and to determine the concentration of Lp(a) accurately, samples with an Lp(a) concentration > 0.70 g/litre were re-assayed at a higher dilution.

### CRP assay

In addition, a smaller number of the thawed paired serum samples were assayed for CRP using an automated wide range but not high sensitivity immunoturbidimetric method (Roche Diagnostics, Lewes, Sussex, UK).

### Fibrinogen assay

The fibrinogen concentration of each pair of recruit samples was determined using the Claus nephelometric assay adapted for an ACL 300 instrument (IL Laboratories, Warrington, UK).<sup>22</sup>

### Albumin and total CK assays

Albumin and total CK values were determined in fresh serum stored at 4°C using automated commercially available enzymatic test kits (Roche Diagnostics).

## RESULTS

Initially, 303 recruits provided "pre" training serum samples and of these 200 recruits completed the training and provided "post" training serum samples. A smaller number of the recruits provided citrated plasma samples needed for the fibrinogen assay (pretraining, n = 243; post training, n = 151). A small number of recruits did not complete the training programme or failed to provide post exercise blood samples; thus, the number of paired results differs between groups.

The ME was designed to push the recruits to the limit of their physical performance. The duration of the ME along with the field conditions resulted in many recruits returning in a state of fatigue, both from prolonged periods of low intensity

**Table 3** Changes in median lipoprotein(a) (Lp(a)) values for each recruit group before/after the military exercise

	N	Before (range)	After (range)	Δ	p Value	Significance
G1	39	0.09 (0.0–0.9)	0.10 (0.0–0.9)	0.01	0.0599	NS
G2	13	0.14 (0.0–1.0)	0.10 (0.0–0.9)	–0.04	0.3384	NS
G3	32	0.15 (0.0–0.7)	0.14 (0.0–0.6)	–0.01	0.1849	NS
G4	15	0.06 (0.0–1.0)	0.06 (0.0–0.9)	0.00	0.2893	NS
G5	36	0.13 (0.0–0.7)	0.11 (0.0–0.7)	–0.02	0.3425	NS
G6	65	0.13 (0.0–0.9)	0.12 (0.0–1.0)	–0.01	0.1317	NS

The figures are median (range) Lp(a) (g/l).

The data show no significant changes in Lp(a) concentration during the acute phase response (days 1 to 3). NS, not significant.

**Table 4** Changes in plasma fibrinogen concentration (mg/dl) for each recruit group before/after the military exercise (ME)

	N	Before (SD)	After (SD)	Δ	p Value	Significance
G1	41	263 (45)	266 (57)	3	0.7112	NS
G2	13	279 (40)	356 (72)	77	0.0011	S
G3	34	253 (48)	339 (85)	86	<0.0001	S
G4	19	270 (49)	311 (53)	41	0.0433	S
G5	33	245 (46)	247 (60)	2	0.9139	NS
G6	27	267 (47)	295 (57)	28	0.0298	S

Values were unchanged 12 hours after the ME, then increased, representing a strong acute phase response. NS, not significant; S, significant.

**Table 5** Changes in serum C reactive protein (CRP) concentration for each recruit group before and up to five days after the military exercise (ME)

	N	Before	After	Δ	p Value	Significance
G1	41	4.3 (1–22)	4.6 (1–48)	0.3	<0.0001	S
G2	13	1.7 (0–13)	1.4 (1–18)	–0.3	0.3652	NS
G3	13	4.1 (2–7)	5.0 (1–50)	0.9	0.2734	NS
G4	15	4.3 (1–20)	3.6 (1–7)	–0.7	0.0785	NS
G5	34	5.8 (2–41)	5.0 (2–8)	–0.8	<0.0001	S
G6	25	5.4 (3–40)	5.2 (1–29)	–0.2	<0.0001	S

Values are median (range) CRP (g/l).

Because the standard method has low precision at low normal values, data were not analysed further.

However, the graphical presentation in fig 1 shows that the CRP changes are consistent with other markers of the acute phase response and that the physical challenges of this study did elicit that response, for all groups sampled, at different times after the final ME.

NS, not significant; S, significant.

physical activity and lack of sleep. The army is well aware that dehydration leads to a loss in performance and can be extremely dangerous. With this in mind, the recruits are encouraged to take on fluids as often as possible during the exercise and significant dehydration is unlikely to have confounded the serum/plasma data recorded.

### Statistical analysis

The Lp(a) concentrations in the high and low CRP groups were compared using a Mann Whitney U test for unpaired, non-parametrically distributed data. The non-parametrically distributed Lp(a) data were log transformed ( $\log_{10}$ ) before analysis and compared using a two tailed Student's paired *t* test. The pre and post exercise fibrinogen and albumin data were analysed using a two tailed Student's paired *t* test, whereas the CRP and total CK data were compared using a Wilcoxon signed rank test.

The parametrically distributed data are displayed in the tables as mean, SD, p value, and degree of significance, whereas the non-parametrically distributed data are displayed as median, range, p value, and degree of significance. The Δ value indicates the mean or median change between the pre and post ME values, where Δ = post – pre. All data transfor-

mations and statistical analyses were performed using the Graphpad Prism software package.

Table 1 shows the mean and SD for those variables measured in the recruits at intake. Blood pressure readings were obtained before and after five minutes of supine rest. There were no significant differences between groups for any of the analytes measured.

Table 2 shows the recruit intake data divided into two groups on the basis of CRP values. The defined low CRP group had values < 5 g/litre, and the high CRP group had values > 5 g/litre. Given the reported association between the APR and Lp(a), the intake data were first analysed to evaluate any relation between raised CRP values and increased Lp(a) concentrations. The results of the Mann Whitney U test showed there was no significant difference between the Lp(a) concentrations of the two CRP groups (*p* = 0.80).

Table 3 shows the changes in median Lp(a) values for each recruit group. The data show no significant changes in Lp(a) concentration during the APR (days 1 to 3). Overall serum Lp(a) concentrations displayed little change in the recruit groups tested. The recruits sampled 24 hours after the ME displayed the biggest changes in Lp(a), but the changes were negative and not significant.

**Table 6** Changes in serum albumin concentration (g/l) for each recruit group before and up to five days after the military exercise, with significant reductions in five of six recruit groups

	N	Before (SD)	After (SD)	$\Delta$	p Value	Significance
G1	41	49.3 (2)	48.7 (3)	-0.6	0.0160	S
G2	9	49.1 (4)	46.7 (2)	-2.4	0.0076	S
G3	12	48.2 (3)	46.6 (3)	-1.6	0.0487	S
G4	15	48.5 (2)	48.5 (2)	0.0	0.9439	NS
G5	39	50.6 (2)	48.5 (4)	-2.1	0.0014	S
G6	41	49.5 (3)	48.0 (3)	-1.5	0.0016	S

NS, not significant; S, significant.

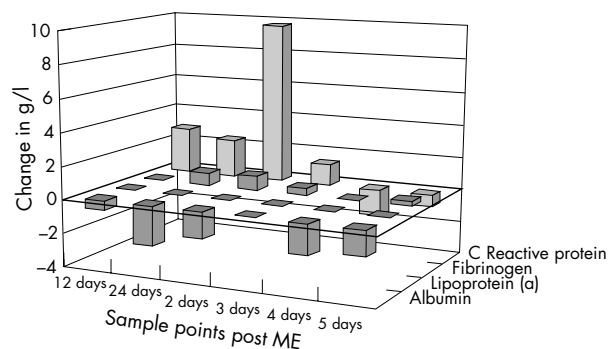
**Figure 1** Mean or median (see text) changes in serum or plasma concentrations of C reactive protein, fibrinogen, lipoprotein (a), and albumin at sampling points from 0.5 to 4 days after completion of the military exercise (ME).

Table 4 shows the changes in plasma fibrinogen concentration for each recruit. Fibrinogen was unchanged 12 hours after the ME, and then values increased significantly on days 1, 2, and 3, representing a strong APR. The plasma concentration of fibrinogen was unchanged in the recruits tested four days post ME, whereas those recruits sampled five days after the ME displayed a small but significant increase.

Table 5 shows the changes in serum CRP concentrations up to five days after the ME. The recruits sampled 12 hours after the ME displayed a significant increase in CRP. The recruits sampled 24 hours, 48 hours, and three days after the ME also showed increases in CRP but these were not significant. Finally, the recruits sampled four and five days post ME showed significant reductions compared with the pre exercise values.

Table 6 shows the changes in serum albumin concentrations that occurred in each recruit group after the ME. Apart from recruits sampled on day three all of the other recruit groups displayed significant reductions in albumin after the ME.

Figure 1 shows the mean/median values for the variables CRP, fibrinogen, Lp(a), and albumin at different time points post ME.

## DISCUSSION

Lp(a) was first described by Berg *et al* in 1963,<sup>24</sup> although the specific functions of this lipoprotein particle have not yet been exactly defined. A moderately above median concentration of Lp(a) (> 0.30 g/litre) is a conditional risk factor, which is dependent on the presence of high associated concentrations of low density lipoprotein, and is reduced with low density lipoprotein reduction<sup>25</sup>; at progressively higher values it acts as an independent risk factor for the development of cardiovascular and cerebrovascular disease.<sup>1,2,19</sup> Given this association, any situation (such as the APR) in which Lp(a) concentrations might increase rapidly, even if only briefly, could influence both the interpretation of Lp(a) results and related decisions in clinical management, and could also contribute to an increased risk of vascular events. The acute phase protein CRP, both alone and in combination with the ratio of total cholesterol to high density lipoprotein cholesterol in serum or plasma, is a powerful marker of cardiovascular risk.<sup>26</sup>

The data presented here show that the intense ME undertaken by the recruits did bring about a clearly defined APR, as demonstrated by rapid changes in several serum proteins accepted as markers of that response. The CRP data were partly qualitative and, similar to the CK data (table 7), may have been compromised by undeclared exercise undertaken by some recruits in preparation for their induction at Basingstoke, and possibly by the intramuscular injections that we later found had been administered at the start of the training period. These complications of the military requirement were outside our control, but it is clear that Lp(a) does not respond in the early acute phase of the APR to extreme physical effort.

Previous reports that Lp(a) concentrations increased in association with markers of an APR to various stimuli did not report an early acute Lp(a) response,<sup>27,28</sup> and were mostly based on observations on small numbers of older subjects, with a wide variety of potentially confounding clinical disorders, including infection, myocardial infarction or angina, and rheumatoid arthritis. There are conflicting reports on the responses of small series of patients to coronary artery bypass and cardiopulmonary bypass surgery.<sup>29,30</sup> The time scale of any change in Lp(a) concentration is also of

**Table 7** Changes in total creatine kinase (CK) activity for each recruit group before and up to five days after the military exercise (ME) (two tailed Wilcoxon signed rank test)

	N	Before	After	$\Delta$	p Value	Significance
G1	41	669 (124-6155)	422 (67-1481)	-74	<0.0001	S
G2	9	690 (127-3188)	452 (120-930)	-34	0.9102	NS
G3	31	333 (160-775)	517 (77-2375)	184	<0.0001	S
G4	15	762 (246-1467)	229 (96-2620)	-533	0.3054	NS
G5	38	1040 (187-4602)	280 (94-1489)	-760	<0.0001	S
G6	60	695 (134-4671)	394 (110-2717)	-301	<0.0001	S

Values are median (range) total CK (U/l).

All of the recruits presented with raised CK values, which were reduced for the recruits sampled 12 hours, 48 hours, and five days after the ME. The recruits sampled after 24 hours and three days also showed some reduction in total CK but changes were not significant.

NS, not significant; S, significant.

**Take home messages**

- In our study lipoprotein (a) (Lp(a)) was not an early marker of the acute response and previous reports may have been confounded by concurrent disease in older subjects or by late sampling
- Lp(a) determination for cardiovascular risk profiling is not confounded by associated physical effort
- It is unlikely that the acute risks of major physical effort are enhanced by processes involving Lp(a)

interest.<sup>31</sup> MBewu *et al* found that Lp(a) values did not change acutely in patients treated with streptokinase after myocardial infarction, but that there may have been a non-significant late increase 14 days after admission.<sup>10</sup> Late increases are also described for patients after myocardial infarction,<sup>11</sup> for patients with idiopathic osteoporosis treated with bisphosphonates,<sup>32</sup> and for patients undergoing chronic haemodialysis.<sup>33</sup>

Most previous studies of exercise or fitness and Lp(a) have involved small groups and have not specifically considered the acute response. Lp(a) was reported to be significantly increased two days after a three hour running test, and after a nine or 12 month exercise programme in previously sedentary and mostly middle aged men and women.<sup>34</sup> The young Finns study<sup>16</sup> found that lower concentrations of Lp(a) were associated with increased amounts of leisure time physical activity. Durstine *et al* showed that there was no immediate effect on Lp(a) values after a short period of treadmill walking,<sup>6</sup> and Hubinger *et al* found that 60 minutes of treadmill running at two different intensities over a period of seven days did not produce differential effects on Lp(a) concentrations.<sup>34</sup> Halle *et al* compared Lp(a) values in endurance and power athletes with those of sedentary controls and found only small differences between the groups.<sup>7</sup> Lobo *et al* reported that Lp(a) values were not affected by exercise or oestrogen treatment in older men and women.<sup>35</sup> Szymanski *et al* showed that Lp(a) values did not correlate with markers of fibrinolytic activity or exercise in healthy men.<sup>36</sup> Overall, these findings indicate that serum Lp(a) values are not acutely (if at all) affected by training, in contrast to fibrinogen.<sup>37</sup> Post infarction changes (if seen) are delayed in comparison with classic APR markers, notably CRP, and it is unlikely that similar cytokine signalling pathways are involved in those responses.<sup>26</sup>

"Most previous studies of exercise or fitness and lipoprotein (a) have involved small groups and have not specifically considered the acute response"

The suggestion that any Lp(a) response to acute effort or other APR stimulus could be delayed or influenced by apo(a) phenotype, which may regulate the post translational rate of assembly of the LDL-apo(a) combined particle, requires further attention.<sup>15</sup> It is also possible that previous data may be confounded by coincident silent or evident ill health and are thus disease driven in the mostly older patient groups involved. Our study examined a large group of young, fit subjects, all medically examined and without the confounding effects of disease. They were then subjected to both acute and prolonged challenges, in response to which Lp(a) did not behave as an early marker of the acute response. The metabolic compensations of the APR are not obviously relevant to endogenous control processes of Lp(a) or to the hypercoagulable state observed in the few hours after strenuous exertion. It is also unlikely that the acute cardiac risks of major physical effort in presumed normal individuals or patients with silent or evident coronary disease are enhanced by any process involving Lp(a) beyond that associated with baseline values, which can also be assessed without compromise by recent physical activity.

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## ECHO.....

## Scoring more hits with HSV



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Using PCR routinely would increase detection of HSV, according to Scoular *et al*, testing a LightCycler real time PCR protocol in a diagnostic laboratory serving a large genitourinary medicine clinic in Glasgow, Scotland.

Scoular *et al* compared performance with routinely used viral culture for identifying HSV. They took two swabs from suspect lesions of patients attending the clinic, one into viral transport medium for standard culture and typing, the other into lysis buffer. PCR was carried out on both samples with the LightCycler, using DNA primers for glycoprotein B gene of HSV-1 and HSV-2. Amplified HSV DNA was identified electronically by its melting point at 92.5°C (±0.5°C). PCR with a hybrid Omnigene was repeated to give sufficient DNA to identify HSV-1 and 2 by analysis of restriction fragments.

In all, 109 of 236 patients with paired samples were HSV positive by PCR or culture: 88 were PCR positive, culture positive; 21 PCR positive, culture negative; none were PCR negative, culture positive. PCR results were identical for swabs taken into transport medium or lysis buffer. The method was superior to culture in detecting more positives in vesicular (+13%), ulcerative (+27%), and crusting (+20%) lesions. All positive results yielded HSV-1 or 2.

LightCycler technology is considered suitable for diagnostic laboratory use: with it, overall detection rate went up by 24%, and its speed over conventional PCR gives a head start to advising patients and improving diagnostic performance.

▲ *Sexually Transmitted Infections* 2002;**78**:21–25.

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D J Byrne, I A Jagroop, H E Montgomery, et al.

*J Clin Pathol* 2002 55: 280-285

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