(Factor Heat Treated

HOUSE MESSAGE

C0000057/1

Armour Pharmaceutical Company Ltd.

To: D. Lewis
M. Cross
K. Dunbar
J. Vanhalle
M. Samuelsson

cc: K.W. Fitch
J.D. Michelmore
A. Sheppard
L. Lucas
P. Harris
R.B. Christie

From: C.R. Bishop

Date: 18th July 1986.

R. B. C.
18 JUL 1986

Re: FACTORATE RECALL - MEDIA RESPONSE

As discussed with you individually, I enclose copies of the New Scientist and Guardian articles of the 17th July on the above mentioned subject.

I have it from an extremely reliable source that both articles were initiated by the actions of Peter Jones and, certainly in the case of the New Scientist, this took the form of him providing them with a copy of our recall/exchange letter together with his comments. This is obvious from the last paragraph of both articles which forms the "pay-off" and is, in my opinion, an attempt to justify his previous outburst at the Newcastle AIDS Conference in February which, you will remember, caused so much consternation to Doctors and patients alike.

It may well be, and it is to be hoped, that the majority of Doctors will view the articles in the light of this objective and the contents immediately discredited. This would appear to be the case from discussions both Mike Cross and myself have had to date with leading Directors.

Nevertheless, I will just elaborate on various points made in the articles starting with the New Scientist:-

NEW SCIENTIST - "AIDS FEAR PROMPTS RECALL OF BLOOD PRODUCTS"

Column 1

We have not recalled "dozens of batches", only batches manufactured before May 1985 (the start of our donor testing programme) were eligible for recall. However, the majority of these, of course, were date expired. The response we have had to date has been from two Centres, Cardiff (13 vials) and Exeter.

The two Britons referred to have not been proven and are still undergoing tests and investigations but there is yet no proof that they developed antibodies as a result of treatment with Armour's FACTORATE.

2/....

The Dutch patient referred to was not, repeat not, a clean virgin patient.

Column 2

The word "infection" is totally misleading since there is no proof that the patient received live or dead virus.

Paragraph 2 : The whole tone of this paragraph is an attempt to undermine Armour's objectives and integrity. Yes we did want to keep the exchange low key in order not to cause adverse publicity and, thus, distress to the patient. We would emphasise that the recall was voluntary and agreed with the Department of Health. The inference in this paragraph is that although we say the recall (which should be exchange) is voluntary, there is some doubt. There is no doubt.

Column 3

Paragraph 2: Agains implies an ineffective treatment against HIV and implies we have gone against the official Elstree recommendations. Elstree are in no position to make any recommendations, theirs is simply the heat treatment method they have adopted. We have ample evidence, both in vitro and in vivo, to justify the faith in our own heat treating procedure in eliminating in excess of 5.5 logs of virus.

The linking of Mike Rodell's statement regarding a review of our heat treating procedure again further undermines the faith in the existing heat treating procedure.

As you know, the new heat treating procedure will only be undertaken when we are perfectly happy that no other problems, for example denaturation and the formation of immune complexes, the stabilisation of existing virus etc., will result. We are now happy with this sitation and half-life and recovery studies are underway and we should have new product available fairly shortly.

This revised procedure is not, again repeat not, an implication of lack of faith in our current procedure with regard to the AIDS virus inactivation, but a further attempt to improve its performance against NANB Hepatitis.

THE GUARDIAN - "SUSPECT FACTOR 8 RECALLED IN AIDS ALERT"

Paragraph 1: Our offer of exchange was in order to supply product in-line with Corporate Policy and to supply a product which is deemed to be "state of the art".

Paragraph 2 : This is simply a crib from the New Scientist and I have already covered the points made.

Dr. Peter Harris was mis-quoted in paragraph 6 and this was not applicable to the U.K. exchange.

3/....

Paragraph 8 & 9 illustrate the support and "sympathy" that we are experiencing from The Haemophilia Society and these two paragraphs are perhaps the most sensible in the whole of the article.

Unfortunately, there is little that one can respond to which would not be interpreted as "emotional and subjective" and without "fueling the fire".

It is our feeling, and that of our advisors, (who include members of the U.K. Haemophilia Centre fraternity) that these articles be treated with the contempt they deserve and, therefore, we propose to take no further action other than discussion by you with individual Doctors who may express some concern which you are in a position to discuss on a sensible level.

Unfortunately, the mention of Dr. Michael Rodell's statment that we are reviewing our heat treatment process now prevents us from preparing an official "defence document/article" to The Lancet, which would not be totally misconstrued by those wishing to cast dispersions on the Armour operation. We can not on the one hand defend our existing treatment and then immediately introduce a new one, although the reasons for introducing the new process are primarily to attack the NANB problem.

However, you are in possession of all the facts which we, obviously, will continue to update you on and we will rely on you to relay the correct factual information to all of your contacts.

Upon receipt of this communication, if you have any questions please give me a ring in the Office on Wednesday, Thursday or Friday of next week (23rd, 24th or 25th).

Regards,

GRO-C

C.R. Bishop.

cc: Master
Day
File

AIDS fear prompts recall of blood products

Steve Connor

AN AMERICAN company last week recalled dozens of batches of factor VIII, the clotting agent in blood, from British haemophilia centres, amid growing fears that it could harbour the AIDS virus. The decision, by Armour Pharmaceuticals, follows a similar recall in the US two weeks ago.

At least two Britons suffering from haemophilia have developed antibodies to the AIDS virus after treatment with Armour's factor VIII. Scientists in Britain warned the government five months ago that the now-standard heat treatment of blood products did not guarantee the elimination of the AIDS virus and that individual screening of batches was essential.

Health officials failed to act and, until last month, the government's Blood Products Laboratory was distributing factor VIII that had not been screened for antibodies to AIDS.

A Dutch patient has also developed antibodies to AIDS a year after treatment with Armour's heat-treated factor VIII. Dutch doctors established that there were no other possible routes for infection. Armour has subsequently found that the batch of factor VIII in question came from an American donor who has since developed AIDS. One of the British cases is believed to have received factor VIII from the same donor.

Armour is anxious to play down the recall of its blood products which it calls a "return for exchange". Haemophilia centres will return old batches of unscreened factor VIII and be given new screened batches. Armour consulted with the Department of Health and Social Security before acting, but says the recall is voluntary. It has also sent out a list of "suspect" batch numbers.

The company says that these batches were all manufactured before it began screening each donation of plasma for antibodies to the AIDS virus. This began in April 1985 in the US, and January 1986 in Britain.

A letter in March to Britain's haemophilia centres from Armour's medical officer, Peter Harris, made it clear that the company did not hold its factor VIII, called factorate responsible for the transmission of AIDS. Harris wrote: "There has been no reported case of AIDS and no reported seroconversions associated with the administration of Factorate to a virgin patient not at risk for AIDS."

Armour heats its factor VIII for 30 hours at 60° C in an effort to destroy the AIDS virus. This is far less than the temperature and period recommended by Britain's Blood Products Laboratory, which heats factor VIII at 80° C for 72 hours. Armour's vice president, Michael Rodell, says that the company is reviewing its procedure.

Since last October, all blood donations in Britain have been screened for the presence of AIDS antibodies. But the Blood Products Laboratory says that it continued to distribute unscreened factor VIII until last month.

The laboratory has between 30 and 50 tonnes of plasma that has not been individually screened and will not now be used to make factor VIII..

In February, Peter Jones, director of the Regional Haemophilia Centre in Newcastle upon Tyne, warned that heat-treated factor VIII may still be infective and that all factor VIII must be individually screened for the presence of AIDS antibodies □

Engineering's teetering supports

MANY weaknesses in the links between university engineering departments and industry are revealed by a new report from the Science and Engineering Research Council (SERC). For example, "academic institutions do not appear to give sufficient recognition to the value of industrially relevant research", and "dissemination of results is not good, and there is little central encouragement to spread information", except in research journals that are often "not read by industry". These observations appear in *Support for Engineering*, a study of work supported by the Engineering Board of SERC, which has spent £390 million (at current prices) over the past 10 years.

The report notes that other government agencies such as the Department of Trade and Industry (DTI) are failing to play their part in funding innovation. It says that the SERC "has been left to pursue activities beyond the point where it would normally have expected to withdraw, because other funding agencies have not taken them up". It calls for a "re-examination of the funding arrangements at SERC's boundaries, particularly those with DTI, the Manpower Services Commission and other government departments".

University research in engineering is said to be much healthier than a decade ago. Most bodies consulted welcomed the new element of "directed" research on which the SERC's extra funds for engineering had been spent. But some, notably the Royal Society, thought that the trend had gone too far.

Another more immediate problem for engineering research, especially in more basic areas, was the difficulty of attracting well qualified graduates to study for PhDs. The report calls for "urgent measures" to correct this. It would, if necessary, settle for fewer stipends, each worth a larger amount.

Two other points: SERC's engineering research is not making much of an impact on small firms, and academic engineering departments have so far missed out on making equipment for "big science" such as space research and particle physics. □

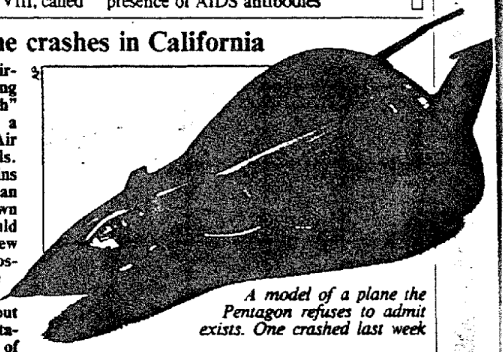
Stealth plane crashes in California

AN EXPERIMENTAL aircraft, probably containing America's latest secret "stealth" technology, was destroyed in a crash last week. The US Air Force refused to give any details.

The shape of stealth remains secret, but designers of such an aircraft would work to known principles. First, they would design an airframe with as few sharp edges or corners as possible. The result would look like a "flying wing".

In the past, flying wings without tail fins were dangerously unstable. Modern techniques of "fly-by-wire", in which a computer helps the pilot keep in control, may overcome this problem.

Another important technology is new materials. Aircraft made from plastics and carbon fibres absorb more radar waves than metal ones do. Special radar-absorbing paints may also help. □



A model of a plane the Pentagon refuses to admit exists. One crashed last week

Success for whaling diplomacy

THE DEPARTMENT of Commerce in the US is expected to notify President Reagan tomorrow of the sanctions it would like imposed on Norway for continuing to kill whales. The department has certified Norway under the Pelly Amendment, which allows the President to ban all fish imports from Norway. This trade is worth £103 million a year.

The International Whaling Commission (IWC) voted in 1982 to end all commercial whaling by 1986. Norway, along with Japan and the USSR, continue to whale. The IWC cannot enforce its decisions, but US sanctions have played a part in bringing countries into line. Nevertheless, in a bilateral agreement, the Commerce Department agreed not to impose sanctions and Japan agreed to quit in 1988. Conservationists sued the US government, arguing that sanctions were mandatory, and won in two lower courts. The Supreme Court, however, on 30 June decided by five to four against them. Japan promptly agreed to end commercial whaling.

Greenpeace dismissed Japan's announcement as an "empty gesture". Japan will continue whaling under the guise of "subsistence fishing" and "scientific research". Norway, too, has said that it will stop commercial whaling, but will then undertake "scientific" whaling until 1990, when the moratorium is due to be re-assessed. Five of the six countries still whaling have said they will continue scientific whaling.

Sidney Holt, one of the foremost experts on whale science, condemns these evasions. "Looking at the entrails of more dead whales will not help," he said. □

Suspect Factor 8 recalled in Aids alert

By Andrew Veitch
Medical Correspondent

The drug firm Armour has withdrawn batches of American-made Factor 8 for haemophiliacs because of fears that it could be carrying the Aids virus, it was disclosed yesterday.

At least four patients — two British, one in the Netherlands and another in the United States—are reported to have been infected after using the Armour product called Factorate.

The Department of Health was consulted about the withdrawal, which came last week, but it made no public announcement.

The department said last night that since the beginning of the year all US Factor 8 given to British patients had come from screened donors.

The withdrawn batches were heat-treated to kill the Aids virus, but the blood plasma from which they were made came from donors who had not been screened. batches of Factorate still on the market come from donors who have been tested for antibodies to the virus.

Armour's medical officer, Dr Peter Harris, said yesterday that the withdrawal was prompted by the Dutch case after one of the donors whose blood plasma was used was found to have been infected.

The two British cases had not been confirmed he added.

Haemophilia centres were being asked to return all Factorate issued before January this year, Dr Harris said.

The Haemophilia Society's co-ordinator, Mr David Watters, said yesterday: "Armour have taken a reasonable, precautionary and voluntary step."

Urging patients to keep taking factor 8, he added that the chance of infection was now very small. "The dangers of bleeding episodes outweigh any other risks."

More than half Britain's 2,000 haemophiliacs have been infected by the virus from contaminated Factor 8 — most of it imported from the US. By the end of May 17 had developed full-blown Aids and 16 of them had died.

The Department of Health was warned five months ago that haemophiliacs might be in danger from Armour's Factor 8.

The warning came from Dr Peter Jones, director of the haemophilia centre at Newcastle-upon-Tyne. He said last night that the product should have been withdrawn earlier.

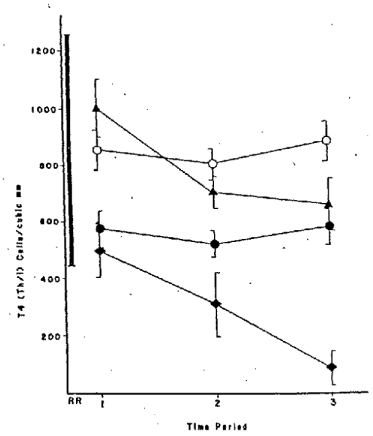


Fig 2—Absolute T4 (Th/i) cell levels for 2-year period.

(Rest of legend as for fig 1.)

still being followed up in 1984–85 have been tested for antibodies to LAV. 38 (42%) were seropositive in 1984–85 and during the two years, AIDS has developed in 5 of these men.

We have analysed T8 and T4 cell counts in four groups of men: (1) those LAV seropositive at all testings since 1982 and AIDS-free; (2) those seronegative at all testings; (3) those who seroconverted within the 2 years; and (4) those who were seropositive and did acquire AIDS within the 2-year period. The average interval between samples was 1 year (range 6–22 months).

Homosexually active males, both LAV positive and negative individuals, showed increased T8 cell counts (fig 1) and the seropositive group had higher counts than the seronegative group. T4 cell levels, however, were lower in the seropositive group (fig 2). The differences between the seropositive and seronegative groups were significant and maintained over a two-year period ($p<0\cdot0003$ for T8 cells, $p<0\cdot0001$ for T4 cells). Of the 16 seropositive individuals without AIDS, only 4 report having had two or more of the symptoms associated with AIDS (such as lymphadenopathy, night sweats, diarrhoea, and weight loss) within the previous two years.

The 12 seroconverter individuals were negative for LAV antibodies at the first point on each graph. Subsequent testing indicated that HTLV-III/LAV infection led to a decrease in T4 cell numbers (fig 2). The seroconverter group changed during the two years from the seronegative to the seropositive range for T4 cells. 9 had a decrease in T4 cell number between the first and third time point, and in 7 the decrease was more than 30%. Although T8 cell counts did not change as sharply after seroconversion as T4 counts did, seroconversion was associated with a rise in T8 cell number. The effect of seroconversion on the T-cell subsets has different dimensions from those reported by Cooper et al,[7] possibly because of the extended length of time in some of our subjects between seroconversion and T-cell testing. A more immediate effect of an increasing T8 count may have been missed in those of our participants who had primary infection soon after their previous visit. The drop in T4, which may not occur as quickly following seroconversion, might not have been detected by Cooper et al because of the shorter interval between infection and testing. The decrease in T4 in the seroconverters does, however, seem to reach an endpoint within the fairly constant range of T4 cells seen in the seropositive group.

The 5 individuals in whom AIDS developed during our study showed (in contrast to the other groups) a progressive lowering of the T4 cell number from normal to distinctly subnormal levels. The T8 cell number increased and then decreased as the total number of lymphocytes fell.

Two patterns of serial T4 cell values were seen in the seropositive groups. In one low normal values were maintained, with limited evidence of clinical deterioration; in the other (those who proceeded to AIDS) T4 cell counts fell progressively. These observations suggest that another factor(s), besides HTLV-III/LAV infection, is needed for substantial lowering of T4 cell levels and progression to the full-blown AIDS.

KENDRA SCHWARTZ
BARBARA R. VISSCHER
ROGER DETELS
JEREMY TAYLOR
PARUNAG NISHANIAN
JOHN L. FAHEY

Schools of Public Health
and of Medicine,
University of California,
Los Angeles, California 90024, USA

1. Barré-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 1983; **220**: 868–70.
2. Popovic M, Sarngadharan MG, Read E, Gallo RC. Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. *Science* 1984; **224**: 497–500.
3. Fahey JL, Prince H, Weaver M, et al. Quantitative changes in T helper or T suppressor/cytotoxic lymphocyte subsets that distinguish acquired immune deficiency syndrome from other immune subset disorders. *Am J Med* 1984; **76**: 95–100.
4. Goedert JJ, Sarngadharan MG, Biggar RJ, et al. Determinants of retrovirus (HTLV-III) antibody and immunodeficiency conditions in homosexual men. *Lancet* 1984; ii: 711–15.
5. Stahl RE, Friedman-Kien A, Dubin R, Marmor M, Zolla-Pazner S. Immunologic abnormalities in homosexual men: relationship to Kaposi's sarcoma. *Am J Med* 1982; **73**: 171–78.
6. Detels R, Fahey JL, Schwartz K, Greene RS, Visscher BR, Gottlieb MS. The relationship between sexual practices and T-cell subsets in homosexually active men. *Lancet* 1983; i: 609–11.
7. Cooper DA, Gold J, Maclean P, et al. Acute AIDS retrovirus infection. Definition of a clinical illness associated with seroconversion. *Lancet* 1985; i: 537–40.

ABSENCE OF ANTIBODIES TO LAV/HTLV-III IN HAEMOPHILIACS TREATED WITH HEAT-TREATED FACTOR VIII CONCENTRATE OF AMERICAN ORIGIN

SIR,—Commercial factor VIII (FVIII) concentrates are now generally heat-treated to reduce the risk of transmission of HTLV-III. Two reports have recorded the absence of antibodies to HTLV-III in patients after treatment with heat-treated FVIII ('Hemofil T', Hyland;[1] and 'Haemate P', Behringwerke).[2] We have looked for anti-HTLV-III in 46 Swedish haemophiliacs after treatment with an American commercial factor VIII concentrate ('Factorate', Armour), which had been heated in lyophilised form for 30 h at 60°C. The plasma donors had not been screened for anti-HTLV-III.

Most Swedish haemophiliacs have now been tested for the anti-HTLV-III. None of those treated exclusively with concentrates of Swedish origin have proved seropositive, whereas about 60% of patients treated with unheated American FVIII concentrates have been found to be anti-HTLV-III positive.

In February, 1985, anti-HTLV-III was found in a Swedish blood donor who had donated plasma for the production of the Swedish FVIII concentrate ('Octonativ', KabiVitrum). Within a few days the then unheated Swedish concentrates were withdrawn from use in haemophilia. At the haemophilia centre in Malmö these concentrates were immediately replaced by heat-treated factorate (batches Y854, Y75204, and A17702), which was then used for over 3 weeks for treating 67 haemophiliacs at doses of about 30 IU/kg body weight twice a week.

Anti-HTLV-III in plasma was sought by enzyme-linked immunosorbent assay (ELISA), either as previously described[3] or with a commercial ELISA test (Organon Teknika), with confirmation by western blotting.[3] Of the 67 haemophiliacs, 21 had anti-HTLV-III in their plasma both before and after treatment with factorate. The remaining 46 patients were all negative for anti-HTLV-III when tested one or more times after start of this treatment; the interval between the start of treatment and the latest anti-HTLV-III test was 3–6 weeks for 10 patients, 7–11 weeks for 9

patients, 12–17 weeks for 12 patients, and 18–23 weeks for 15 patients (mean 12·6 weeks). Thus, no seroconversion to the anti-HTLV-III positive state occurred in the observation period after introduction of heat-treated factorate.

Departments of Coagulation Disorders and Clinical Virology, University of Lund, General Hospital, S-21401 Malmö, Sweden
PETER FELDING
INGA MARIE NILSSON
BENGT GÖRAN HANSSON

Department of Immunology, National Bacteriological Laboratory, Stockholm
GUNNEL BIBERFELD

1. Rouzioux C, Chamaret S, Montagnier L, et al. Absence of antibodies to AIDS virus in haemophiliacs treated with heat-treated factor VIII concentrate. *Lancet* 1985; ii: 271–72.
2. Mösseler J, Schimpf K, Auerswald G, et al. Inability of pasteurised factor VIII preparations to induce antibodies to HTLV-III after long-term treatment. *Lancet* 1985; i: 1111.
3. Biberfeld G, Böttiger B, Karlsson A, et al. HTLV-III infection in homosexuals and hemophiliacs in Sweden. *Cancer Res* (in press).

PROGNOSTIC INDICES IN ACUTE PANCREATITIS

SIR,—In Mr Corfield and colleagues' comparison of three prognostic indices in acute pancreatitis (Aug 24, p 403) it is unfortunate that 40% of patients had to be excluded from one limb of the study. The remaining 60% were then randomised to therapeutic trial, the negative results of which[1] are not alluded to.

But it is in the results section that confusion runs riot. In the clinical assessment section, 10 patients have died without trace. In the multiple laboratory criteria section, 12 deaths not among those graded severe are passed over without comment. In the peritoneal lavage section there were 30 deaths, 21 in the severe prediction group and none in the mild prediction group. Where are the other 9? How were the interdependent prognostic indices summated? The term "serious complications" sometimes includes and sometimes excludes deaths and the close juxtaposition of the phrases "attacks that were severe" and "attacks graded as severe" is confusing.

University Hospital, Queen's Medical Centre, Nottingham NG7 2UH
P. W. WENHAM
C. S. ROBERTSON

1. Mayer AD, McMahon MJ, Corfield AP, et al. Controlled clinical trial of peritoneal lavage for the treatment of severe acute pancreatitis. *N Engl J Med* 1985; **312**: 399–404.

SIR,—Mr Corfield and colleagues report that both multiple laboratory criteria and peritoneal lavage are more sensitive than clinical assessment on admission in detecting severe and ultimately fatal cases of acute pancreatitis. Combining the three indices, such that outcome would be predicted as severe if any one index was positive, increased the sensitivity still further. Corfield et al suggest that this information should be useful in setting up prospective therapeutic trials when a specific therapy for the disease becomes available.

However, Corfield et al failed to point out that, despite the increased sensitivity, the improvement in the predictive value of a positive result using these indices is trivial or non-existent (see table). The predictive value of positive multiple laboratory test results, which take up to 48 hours to accumulate, is only marginally better than an early clinical assessment (58·9% versus 54·3%). The increased predictive value of an abnormal peritoneal lavage (62·3%) is entirely attributable to the increased prevalence (31·7% versus 25·5%) in the population selected for this invasive technique. In the whole population of 435, the predictive value for severe disease when any one of the three indices is abnormal is actually lower than that for early clinical assessment alone (51·8% versus 54·3%). It is not possible from the published data to calculate predictive values from the 56% of patients in whom all three prognostic indices were assessed.

The message is clear. Whatever index, or combination of indices, is used, less than 60% of patients predicted to have a severe outcome will indeed turn out to have such. This must be borne in mind when setting up a prospective therapeutic trial, in order to avoid unwarranted benefits being ascribed to a given specific therapy.

Department of Chemical Pathology, St James's University Hospital, Leeds LS9 7TF
I. R. GUNN

**These letters have been shown to Professor Williamson and his colleagues, whose reply follows.—ED. L.

SIR,—Dr Gunn's letter shows that all existing prognostic indices overdiagnose severity in acute pancreatitis, and we accept his caveat about therapeutic trials. The fact remains that initial clinical assessment picks up less than half the patients destined to die during the same hospital admission. This percentage is surely unacceptable. We believe that it is better to monitor and treat some patients with unnecessary vigour than to miss the "occult severe" patients whose life might be saved by aggressive management. Thus for the clinician sensitivity is more important than the predictive value of a positive result. We should also consider the possibility that some of our patients initially graded as "severe" turned out to have a mild attack as a direct result of the care and attention they received because of this label.

Let us now examine the substance of the charges laid by Mr Wenham and Mr Robertson. We plead guilty to one typographical error. In the clinical assessment section there were 19 deaths among the "severe" group but 22 deaths (not 12) among the "mild" group: here are the 10 missing deaths. By contrast, in the peritoneal lavage section it is not our mathematics that is defective but your Nottingham correspondents' reading of the text. Of 30 deaths, 21 were in the severe prediction group and 9 in the mild prediction group. It was only among the subset of "mild" patients with pale free fluid (n=27) that there were no deaths. Our paper was concerned with the fact of death in these patients and not the manner of their passing—otherwise it would have been twice as long.

The prognostic indices were not interdependent. They were summated by considering the outcome of patients in whom any one

ABILITY OF PROGNOSTIC INDICES TO PREDICT SEVERE OUTCOME

	Predicted outcome by:							
	Clinical index		Laboratory index		Lavage index		Multiple criteria prediction	
Outcome	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe
Severe (n=111)	73	38	41	63	37	43	26	85
Mild (n=324)	292	32	249	44	146	26	245	79
Total (n=435)	365	70	290	107	183	69	271	164
Sensitivity	*34·2%*		*60·6%*		*53·8%*		*76·6%*	
Specificity	*90·1%*		*85·0%*		*84·8%*		*75·6%*	
Predictive value of positive	*54·3%*		*58·9%*		*62·3%*		*51·8%*	
Predictive value of negative	*80·0%*		*85·9%*		*79·8%*		*90·4%*	
Prevalence of severe outcome	*25·5%*		*26·2%*		*31·7%*		*25·5%*	