CLINICAL RESEARCH

# Failure of delayed hypersensitivity skin testing to predict postoperative sepsis and mortality

ROGER BROWN, JOHN BANCEWICZ, JAWED HAMID, NAREN J PATEL, CAROL A WARD, ROGER J FARRAND, RICHARD S H PUMPHREY, MILES IRVING

## Abstract

**Delayed hypersensitivity skin reactions to a battery of recall antigens, haemoglobin and albumin concentrations, arm-muscle circumference, and percentage of ideal weight were determined before operation in 244 patients undergoing elective major surgery.**

**Depressed skin reactions were found in 70 patients (28%), but this group did not have significantly higher sepsis or mortality rates when compared with patients with normal reactions. Significant associations were found between depressed skin reactions and increasing age, anaemia, hypoalbuminaemia, low arm-muscle circumference, and low weight. Patients with benign and malignant disease had similar distributions of skin reactions. Hypoalbuminaemia was associated with a higher rate of serious postoperative sepsis, and hypoalbuminaemia, low arm-muscle circumference, and low weight were all associated with a higher mortality.**

**These results suggest that the routine use of delayed hypersensitivity skin testing in the preoperative assessment of surgical patients is not justified.**

**Hope Hospital, University of Manchester Medical School, Salford M6 8HD**

ROGER BROWN, FRCS, tutor in surgery
JOHN BANCEWICZ, FRCS, senior lecturer in surgery
JAWED HAMID, PHD, postdoctoral immunologist
NAREN J PATEL, PHD, microbiology technician (present appointment: research microbiologist, Dyson Perrins Laboratories, University of Oxford, Oxford OX1 3QY)
CAROL A WARD, immunology technician
ROGER J FARRAND, MA, FRCPATH, consultant microbiologist (present appointment: consultant microbiologist, Bolton Royal Infirmary, Bolton BL1 4QS)
RICHARD S H PUMPHREY, MRCPATH, consultant immunologist (Manchester Royal Infirmary)
MILES IRVING, MD, FRCS, professor of surgery

## Introduction

Despite the strict application of aseptic and antiseptic techniques and a more rational approach to the use of antibiotics, sepsis remains an important cause of morbidity and mortality in patients undergoing surgery. The preoperative identification of patients at particular risk of developing septic complications would be invaluable. Diminished host resistance may be a major factor in the development of sepsis, and the immune state of patients has therefore been increasingly studied. MacLean *et al*,[1-4] Johnson *et al*,[5] and Kune[6] reported on the value of delayed hypersensitivity skin testing in predicting septic complications. They found that failure to react to a battery of recall antigens (anergy) was associated with an increased risk of sepsis and death. Such skin testing is easily performed in routine clinical practice and is now widely used in North America.

Daly *et al* showed that protein depletion may produce anergy in animals but that skin reactivity may be restored by protein repletion.[7] Anergy is commonly associated with malnutrition, and skin testing is now widely used as an index of nutritional state.[8-10]

We assessed the value of skin testing and some other nutritional indices in predicting sepsis and death in our own surgical patients.

## Patients and methods

Delayed hypersensitivity skin tests were carried out on 244 patients admitted to this hospital for elective major surgery. Table I summarises the diagnoses of the patients studied. Patients with biliary or pancreatic disease underwent a procedure greater than simple cholecystectomy. The age range of the patients was 16 to 84 years (median 57); 161

TABLE I—*Diseases diagnosed in 244 patients undergoing major elective surgery*

| | Malignant | Acid/peptic ulcer | Biliary/ pancreatic | Inflammatory bowel | Other |
|---|---|---|---|---|---|
| No (%) of patients | 106 (43) | 53 (22) | 31 (13) | 31 (13) | 23 (9) |

(66%) of the patients were aged over 50 years and 114 (47%) over 60 years.

*Skin testing*—Skin testing was performed using 0·1 ml intradermal injections of each of five recall antigens: tuberculin purified protein derivative (1000 units/ml, Evans Medical Ltd); Varidase (streptokinase 100 units/ml + streptodornase 25 units/ml, Lederle); mumps skin-test antigen (undiluted, Eli Lilly and Co); 1% *Candida albicans* (undiluted, Bencard); and 1% trichophyton mixture (undiluted, BV Hal, Allergenen Laboratorium, Haarlem, Holland). A control injection of 0·1 ml buffered diluent solution (Bencard) was also given. All injections were given into the forearm. At each injection site, induration greater than 5 mm diameter at 24 or 48 hours was considered to be a positive reaction. The patients were classified as normal (two or more positive reactions), relatively anergic (one positive reaction), and anergic (no positive reaction), as described by Meakins *et al.*[3]

*Nutritional measurements*—Height and weight were measured before operation and the percentage of the ideal weight derived from standard tables. Haemoglobin and serum albumin concentrations were determined. Midarm circumference and triceps skinfold thickness were measured on the non-dominant arm, and the arm-muscle circumference calculated.[11] Arm-muscle circumference was considered to be low if it was more than two standard deviations below the normal range established for our hospital population.

*Bacteriology*—All complications were recorded and strenuous efforts made to identify the organisms, including anaerobes, responsible for sepsis.

*Statistical calculations* were performed using the $\chi^2$ test with Yates's correction for small numbers and the Mann-Whitney U test.

## Results

Table II shows the distribution of patients' skin reactions and the major sepsis, total sepsis, and mortality rates for each group. Major sepsis was defined as the development of an intra-abdominal abscess or septicaemia. Total sepsis included wound, chest, and urinary tract infections in addition to major sepsis. No significant differences were found in the sepsis and mortality rates among the three groups. The age of patients with normal reactions was lower than that of the relatively anergic group ($p < 0·001$) and of the anergic group ($p < 0·001$).

Table III shows the relation between age and reactions to skin tests. Of the 114 patients aged over 60, 51 (45%) had depressed reactions (anergic or relatively anergic); this was a significantly greater proportion than in those aged below 40 ($p < 0·001$) and those aged 40-59 ($p < 0·001$).

TABLE II—*Rates of sepsis and death in the three groups of patients*

| | Normal (n = 174) | Relatively anergic (n = 32) | Anergic (n = 38) |
|---|---|---|---|
| Median age (range) in years | 54 (16–82) | 66 (21–84) | 68 (29–82) |
| No (%) who died | 11 (6·4) | 4 (12·5) | 6 (15·8) |
| No (%) with major sepsis | 16 (9·2) | 2 (6·2) | 4 (10·5) |
| No (%) with total sepsis | 55 (31·6) | 9 (28·1) | 15 (39·4) |

TABLE III—*Relation between age and reaction to skin tests. Figures are numbers of patients (percentages in parentheses)*

| Age group (years) | No of patients | Normal (n = 174) | Relatively anergic (n = 32) | Anergic (n = 38) |
|---|---|---|---|---|
| >60 | 114 | 63 (55·3) | 24 (21·2) | 27 (23·7) |
| 40–59 | 81 | 68 (84·0) | 5 (6·2) | 8 (9·8) |
| <40 | 49 | 43 (87·8) | 3 (6·1) | 3 (6·1) |

TABLE IV—*Relation between age, sepsis, and death. Figures are numbers of patients (percentages in parentheses)*

| Age group (years) | No of patients | Major sepsis | Total sepsis | Deaths |
|---|---|---|---|---|
| >60 | 114 | 9 (7·9) | 44 (38·6) | 16 (14·0) |
| 40–59 | 81 | 10 (12·3) | 28 (34·6) | 5 (6·2) |
| <40 | 49 | 3 (6·1) | 7 (14·2) | 0 |

TABLE V—*Relation between age, sepsis, and death in patients with depressed skin reactions (percentages of patients in parentheses)*

| Age group (years) | No of patients | Major sepsis | Total sepsis | Deaths |
|---|---|---|---|---|
| >60 | 51 | 4 (7·8) | 20 (39·2) | 9 (17·6) |
| 40–59 | 13 | 2 (15·4) | 3 (23·1) | 1 (7·7) |
| <40 | 6 | 0 | 1 (16·7) | 0 |

TABLE VI—*Relation between nutritional variables and skin reaction (percentages of patients in parentheses)*

| | Normal (n = 174) | Relatively anergic (n = 32) | Anergic (n = 38) |
|---|---|---|---|
| Haemoglobin < 12 g/dl | 37 (21·4) | 14 (43·7) | 13 (34·2) |
| Albumin < 35 g/l | 23 (13·2) | 10 (31·2) | 18 (48·6) |
| Weight < 80% ideal | 19 (10·9) | 5 (15·6) | 10 (26·3) |
| Low arm-muscle circumference | 26 (14·9) | 8 (25·0) | 11 (28·9) |

TABLE VII—*Rates of sepsis and mortality related to nutritional variables (percentages of patients in parentheses)*

| Nutritional variable | | No of patients | Major sepsis | Total sepsis | Deaths |
|---|---|---|---|---|---|
| Haemoglobin | < 12 g/dl | 64 | 6 (9·4) | 21 (32·8) | 8 (12·5) |
| | > 12 g/dl | 180 | 16 (8·9) | 58 (32·2) | 13 (7·2) |
| Albumin | < 35 g/l | 51 | 9 (17·6) | 17 (33·3) | 12 (23·5) |
| | > 35 g/l | 192 | 13 (6·8) | 62 (32·3) | 9 (4·7) |
| Weight | < 80% ideal | 34 | 3 (8·8) | 14 (41·2) | 9 (26·5) |
| | > 80% ideal | 210 | 19 (9·0) | 65 (31·0) | 12 (5·7) |
| Arm-muscle circumference | Normal | 45 | 4 (8·9) | 17 (37·8) | 8 (17·8) |
| | Below normal | 199 | 18 (9·0) | 62 (31·2) | 13 (6·5) |

The rate of major sepsis was not affected by age (table IV) but there was a higher rate of total sepsis in patients over 40 years ($p < 0·01$) and a higher mortality in patients over 60 years ($p < 0·05$). Patients with depressed skin reactions showed similar differences in the three age groups (table V).

The distribution of skin reactions in patients with malignant disease was identical with that in patients with benign disease. The major and total sepsis rates were similar in patients with benign and malignant disease, but patients with malignant disease had a higher mortality (17% *v* 2%; $p < 0·001$). The median age of patients with malignant disease was 66 years compared with 49 years for patients with benign disease.

Table VI shows the relations between nutritional variables and skin reaction. Patients with depressed reactions had higher prevalences of anaemia ($p < 0·01$), hypoalbuminaemia ($p < 0·001$), low weight ($p < 0·05$), and low arm-muscle circumference ($p < 0·05$) than patients with normal reactions. Table VII shows the relations of these variables to postoperative sepsis and death. There was a higher mortality in patients with hypoalbuminaemia ($p < 0·001$), low ideal weight ($p < 0·001$), and low arm-muscle circumference ($p < 0·01$) compared with patients with normal values. In addition, patients with hypoalbuminaemia had a higher incidence of major septic complications ($p < 0·05$). Total sepsis rates were not affected by any of the nutritional variables.

## Discussion

Our results are clearly at variance with those of Meakins *et al*,[3] Kune,[6] and Johnson *et al*[5] with pronounced variations in the proportion of patients found to be anergic: Meakins *et al* found only 5%, Johnson *et al* 31%, and Kune 38% in contrast to our 16%, despite all the studies being on patients of similar age undergoing elective major surgery. The proportion of anergic patients developing sepsis in the other studies was also variable, whereas we could find no difference in the incidence of sepsis among our three groups of patients.

The delayed hypersensitivity reaction is a cell-mediated phenomenon including antigen processing by macrophages, activation of memory T lymphocytes, and the release of soluble

factors that mediate the ensuing hypersensitivity reaction. Christou and Meakins[12] suggested that anergy in surgical patients may be due to the presence of serum inhibitors of lymphocyte chemotaxis that also decrease neutrophil chemotaxis. Johnson *et al*[13] found that 13 out of 14 patients with cancer (anergic to 2,4-dinitrochlorobenzene) failed to react to a topical application of croton oil, suggesting that anergy may be due to a failure of the inflammatory reaction, without implicating a defect in specific cell-mediated mechanisms. Hence cutaneous anergy is not necessarily the result of a defect in cell-mediated immunity and its relation to sepsis and mortality in some groups of surgical patients may be considered to be an epiphenomenon.

There is further evidence that depressed skin reactions and increased sepsis may be an association rather than cause and effect. In anergic and relatively anergic patients, Meakins *et al*[3] reported a mortality of 33% but a sepsis rate of only 20%, the excess mortality obviously being the result of non-septic complications. Similarly, Johnson *et al*[13] found a higher rate of non-septic complications in anergic patients.

The concept and importance of "relative anergy" is also debatable. It is defined operationally as a positive skin reaction to only one antigen, and this is difficult to reconcile with the accepted conceptual framework of cell-mediated immunity. Even a single positive reaction indicates an intact cell-mediated immune response. Failure to respond to additional antigens implies lack of previous exposure or the development of specific suppression mechanisms. Specific suppression mechanisms are not usually considered important in the acquired anergy of surgical patients, which is usually thought to be a non-specific phenomenon.

The variations between our results and those of others may be explained by differences in the incidence of anergy in the general populations from which patient groups were drawn, in the severity and incidence of various disease states, and in the antigen sources and doses used. The most notable difference among our groups was the greater age of anergic and relatively anergic patients. It has been stated that below 80 years, reactions to skin tests are unaffected by age[2] but in this study depressed reactions were commoner in patients over 60 than in those under 60. This is not an effect of malignant disease, which was commoner in the older age group, because patients with benign and malignant disease had similar reactions. The higher total sepsis rate in patients over 40 years was attributable to a higher incidence of chest infections, which, in most of our patients, was a manifestation of pre-existing lung disease rather than of any immune defect.

Many studies have convincingly shown the adverse effect of gross malnutrition on various aspects of the immune response,[14 15 16] and the consequences of this in the Third World countries are well known.[16 17] We found some relation between malnutrition and anergy, but hypoalbuminaemia, low weight, and low arm-muscle circumference were better pointers to an increased mortality rate. Only hypoalbuminaemia was associated with an increased incidence of major sepsis. Serum albumin concentration is not a reliable guide to total body albumin, however, and may reflect existing sepsis rather than malnutrition, even in patients undergoing elective surgery.

The relation between malnutrition and cutaneous anergy has been clearly established in animals.[7] Anergy in surgical patients, however, is likely to be due to factors other than malnutrition, and the suggestion that all anergic patients require total parenteral nutrition before elective operation[2] should be viewed with some caution.

We have not confirmed the higher risks of anergic patients. It seems to us unjustifiable to submit large numbers of pre-operative patients to the considerable discomfort of these expensive tests until things have been clarified. We conclude that there is no indication for the widespread use of delayed hypersensitivity skin testing in preoperative patients.

This work was carried out with the support of a grant from the Wellcome Trust.

We are grateful to Professor W Ford, University of Manchester, and Professor H B Stoner, MRC Trauma Unit, for helpful advice, and to the consultant surgeons of Hope Hospital for permission to study their patients.

## References

1 MacLean LD, Meakins JL, Taguchi K, Duignan JP, Dhillon KS, Gordon J. Host resistance in sepsis and trauma. *Ann Surg* 1975;**192**: 207-17.
2 Meakins JL, Christou NV, Shizgal HM, MacLean LD. Therapeutic approaches to anergy in surgical patients. *Ann Surg* 1979;**190**:286-96.
3 Meakins JL, Pietsch JB, Bubenick O, *et al*. Delayed hypersensitivity: indicator of acquired failure of host defences in sepsis and trauma. *Ann Surg* 1977;**186**:241-50.
4 Pietsch JB, Meakins JL, MacLean LD. The delayed hypersensitivity response: application in clinical surgery. *Surgery* 1977;**92**:349-55.
5 Johnson WC, Ulrich F, Meguid MM, *et al*. Role of delayed hypersensitivity in predicting postoperative morbidity and mortality. *Am J Surg* 1979;**137**:536-42.
6 Kune GA. Life threatening surgical infection: its development and prediction. *Ann R Coll Surg Engl* 1978;**60**:92-8.
7 Daly JM, Dudrick SJ, Copeland EM. Effect of protein depletion and repletion on cell mediated immunity in experimental animals. *Ann Surg* 1978;**188**:791-6.
8 Blackburn GL, Bistrian BR, Maini BS, Schlamm HT, Smith MF. Nutritional and metabolic assessment of the hospitalised patient. *JPEN* 1977;**1**:11-22.
9 Daly JM, Dudrick SJ, Copeland EM. Intravenous hyperalimentation. Effect on delayed cutaneous hypersensitivity in cancer patients. *Ann Surg* 1980;**192**:587-92.
10 Mullen JL, Buzby GP, Waldman MT, Gertner MH, Hobbs CL, Rosato EF. Prediction of operative morbidity and mortality by preoperative nutritional assessment. *Surg Forum* 1979;**30**:80-2.
11 Gurney JM, Jelliffe DB. Arm anthropometry in nutritional assessment; nomogram for rapid calculation of muscle circumference and cross-sectional muscle and fat areas. *Am J Clin Nutr* 1973;**26**:912-5.
12 Christou NV, Meakins JL. Delayed hypersensitivity in surgical patients: a mechanism for anergy. *Surgery* 1979;**86**:78-85.
13 Johnson MW, Maibach HI, Salmon SE. Skin reactivity in patients with cancer. *N Engl J Med* 1971;**284**:1255-6.
14 Copeland EM, MacFadyen BV, Dudrick SJ. Effect of intravenous hyperalimentation on established delayed hypersensitivity in the cancer patient. *Ann Surg* 1976;**184**:60-4.
15 Haffejee AA, Angorn IB, Brain PP, Duursma J, Baker LW. Diminished cellular immunity due to impaired nutrition in oesophageal carcinoma. *Br J Surg* 1978;**65**:480-2.
16 Chandra RK. Rosette-forming T lymphocytes and cell-mediated immunity in malnutrition. *Br Med J* 1974;iii:608-9.
17 Chandra RK. Immunocompetence in undernutrition. *J Pediatr* 1972;**81**: 1194-200.

(*Accepted 24 November 1981*)

---

ONE HUNDRED YEARS AGO The prevalent dyspepsia from which Americans suffer so much, and which is so apt to undermine the strength of the men and the bloom of the women of America, is in a large measure due, we believe, to the universal habit of drinking large quantities of ice-water. This essentially transatlantic habit has long been a speciality of which our American friends and travellers seem to be proud, complaining that they find the purest water in England undrinkable, from the difficulty of getting water to drink with lumps of ice floating about in it. Nothing can be more destructive to the utility of the process of digestion than this habit. There is, however, another danger inherent in this mode of introducing ice, to which attention has more than once been called by sanitary authorities in this country, and which, we note with interest, is now also attracting notice in America. It hardly needed the scientific experiments of Professor Pumpelly—an authority whose name is singularly appropriate to the investigation—to prove again that the freezing of organic impurities and diseased germs does not deprive them of vitality, but only suspends their activity; and that frozen water is apt to entangle a large proportion of the floating impurities, which may be suspended in it; and that it is probably quite as easy to contract typhoid fever from impure ice, as from impure water. The habit of drinking ice-water is altogether a bad one, and may readily become a source of serious or fatal illness if the ice be impure. (*British Medical Journal*, 1882.)