The Department of Health together with Trent Regional Health Authority is presently funding a careful evaluation of lithotripsy with a randomised controlled trial.[8] Let us be patient and await its outcome.

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1 Hood KA, Keightley A, Dowling RH, Dick JA, Mallinson CN. Piezo-ceramic lithotripsy of gallbladder stones: initial experience in 38 patients. *Lancet* 1988;i:1322-4.
2 Sackmann M, Delius M, Sauerbruch T, *et al*. Shock-wave lithotripsy of gallbladder stones: the first 175 patients. *N Engl J Med* 1988;**318**:393-7.
3 Ponchon T, Martin X, Mestas JL, Cathignol D, Lambert R. Gallbladder lithotripsy: preliminary results in 13 patients. *Gastroenterol Clin Biol* 1987;**11**:832-3.
4 Bland KI, Jones RS, Maher JW, *et al*. Extracorporeal shock-wave lithotripsy of bile duct calculi. An interim report of the Dornier US bile duct, lithotripsy prospective study. *Ann Surg* 1989;**6**:743-53.
5 Challah LS, Mays NB. The randomised controlled trial in the evaluation of new technology: a case study. *Br Med J* 1986;**292**:877-8.
6 Charig CR, Webb DR, Payne SR, Wickham JEA. Comparison of treatment of renal calculi by open surgery, percutaneous nephrolithotomy, and extracorporeal shock-wave lithotripsy. *Br Med J* 1986;**292**:879-82.
7 Mays N, Challah S, Patel S, *et al*. Clinical comparison of extracorporeal shock-wave lithotripsy and percutaneous nephrolithotomy in treating renal calculi. *Br Med J* 1988;**297**:253-8.
8 Milner DC, Nicholl J, Westlake L, *et al*. The design of a randomized controlled trial for the evaluation of lithotripsy as a treatment for gallstones. *Journal of Lithotripsy and Stone Disease* 1989;**1**:122-32.

Breast cancer and a proto-oncogene

C-erbB-2 is a reliable prognostic marker

Proto-oncogenes encode proteins that have a normal function, but when these genes are altered or expressed abnormally they contribute to the pathogenesis of cancer. The proto-oncogene c-erbB-2 (neu, HER2, NGL) encodes a protein with a structure that indicates that it is a transmembrane growth factor receptor. Its amplification in human adenocarcinoma was reported in 1986,[1] and one year later Slamon *et al* reported that the gene was amplified in some 30% of carcinomas of the breast and that this amplification was associated with a poor prognosis.[2] Shortly afterwards Venter *et al* reported that gene amplification was associated with increased formation of the c-erbB-2 protein—shown immunohistochemically on frozen tissue sections.[3] How this knowledge might be used in managing patients with breast cancer is the subject of much current research.

Further studies using either DNA analysis or immunohistochemistry have reported the proportion of patients with c-erbB-2 amplification as between 10% and 30%, but until recently fewer than 200 patients had been included in any one study so confidence intervals were wide. Associations have been found with tumour size and tumour grade, amplification of the oncogene being most frequent in large,[4] poorly differentiated carcinomas.[5-7] Other reports relating to c-erbB-2 to recognised prognostic factors have been inconsistent.

Some of the small studies have found a relation between c-erbB-2 and poor prognosis[7-9] and some have not.[4 5 10 11] Material from over 500 tumours, however, has now been examined by each of two groups.[6 12] Both found a correlation between c-erbB-2 and a poor outcome. Slamon *et al* have carried out the most comprehensive work so far, in which the oncogene and its products (RNA and protein) were examined in 526 patients.[12] Three hundred and forty five of the women had positive nodes, and in a multivariate analysis c-erbB-2 was found to be an independent negative predictor of both survival free of disease and overall survival. Unfortunately, the grade of tumour was not included in this analysis. No association between c-erbB-2 and prognosis was found in the 181 patients with negative nodes. The other study, on 602 patients with breast cancer, also showed that the presence of c-erbB-2 protein was an adverse prognostic factor.[6] The relation between amplification of c-erbB-2 and poor prognosis seems to be real, but the marker is only informative in the minority of women in whom the gene is amplified.

Immunohistochemical studies have several advantages over studies that examine oncogenes at the DNA level. Tumour tissue can be differentiated from surrounding stroma, and the expression of the oncogene product within specific parts of the tumour can be examined. At the end of 1988 van de Vijver *et al* showed that 42% (19) of samples from 45 in situ ductal carcinomas stained positively for the c-erbB-2 protein.[4] Strikingly, all the specimens that stained positively were of comedo type and were composed of large pleomorphic cells. A similar association between large cell size and amplification of c-erbB-2 has been reported for invasive carcinomas[13] and for Paget's disease of the nipple.[14] In most of the women with Paget's disease the in situ component of the underlying carcinoma was of comedo type, and the oncoprotein was present in 41 of 45 (91%) of them. This association between amplification of an oncogene and morphological type of carcinoma was predicted by Cardiff, who also foresaw that patterns of staining with antibodies against oncogene products could be a useful new way of classifying mammary carcinoma.[15]

The importance of c-erbB-2 has yet to be fully evaluated in comparison with existing prognostic factors in breast cancer. Will this marker be more useful than the best of the existing factors, such as tumour grade when consistently assessed and S-phase fraction measured by flow cytometry?[16 17] Although showing that an oncogene product is related to outcome is clearly exciting, it does not necessarily provide more information than that given by well established methods. The search for new and better prognostic factors must, however, continue so that optimal treatment can be selected for individual patients.

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1 Yokota J, Toyoshima K, Sugimara T, *et al*. Amplification of c-erbB-2 oncogene in human adenocarcinomas in vivo. *Lancet* 1986;i:765-7.
2 Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;**235**:177-82.
3 Venter DJ, Kumar S, Tuzi NL, Gullick WJ. Overexpression of the c-erbB-2 oncoprotein in human breast carcinomas: immunohistological assessment correlates with gene amplification. *Lancet* 1987;ii:69-72.
4 Van de Vijver MJ, Peterse JL, Mooi WJ, *et al*. Neu-protein overexpression in breast cancer: association with comedo-type ductal carcinoma in situ and limited prognostic value in stage II breast cancer. *N Engl J Med* 1988;**319**:1239-45.
5 Barnes DM, Lammie GA, Millis RR, Gullick WJ, Allen DS, Altman DG. An immunohistochemical evaluation of c-erbB-2 expression in human breast carcinoma. *Br J Cancer* 1988;**58**:448-53.
6 Lovekin C, Ellis IO, Locker A, *et al*. cERB2 oncogene expression in breast cancer: relationships and prognostic significance. *J Pathol* 1989;**158**:345.
7 Wright C, Angus B, Nicholson S, *et al*. Expression of c-erbB-2 oncoprotein: a prognostic marker in human breast cancer. *Cancer Res* 1989;**49**:2087-91.
8 Varley JM, Swallow JE, Brammar WJ, Whittaker JL, Walker RA. Alterations to either c-erbB-2 (neu) or c-myc proto-oncogenes in breast carcinomas correlate with poor short term prognosis. *Oncogene* 1987;**1**:423-30.
9 Berger MS, Locher GW, Saurer S, *et al*. Correlation of c-erbB-2 gene amplification and protein expression in human breast carcinoma with nodal status and nuclear grading. *Cancer Res* 1988;**48**:1238-43.

10 Ali IU, Campbell G, Lidereau R, Callahan R. Amplification of c-erbB-2 and aggressive human breast tumours? *Science* 1988;**240**:1795-6.
11 Gusterson BA, Machin LG, Gullick WJ, *et al.* C-erbB-2 expression in benign and malignant breast disease. *Br J Cancer* 1988;**58**:543-8.
12 Slamon DJ, Goldolphin W, Jones LA, *et al.* Studies of HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989;**244**:707-12.
13 Borg A, Linell F, Idvall I, *et al.* HER2/neu amplification and comedo type breast carcinoma. *Lancet* 1989;i:1268-9.
14 Lammie GA, Barnes DM, Millis RR, Gullick WJ. An immunohistochemical study of the presence of c-erbB-2 protein in Paget's disease of the nipple. *Histopathology* (in press).
15 Cardiff RD. Cellular and molecular aspects of neoplastic progression in the mammary gland. *Eur J Cancer Clin Oncol* 1988;**24**:15-20.
16 Clark GM, Dressler LG, Owens MA, *et al.* Prediction of relapse or survival in patients with node-negative breast cancer by DNA flow cytometry. *N Engl J Med* 1989;**320**:627-33.
17 O'Reilly SM, Camplejohn RS, Barnes DM, Millis RR, Richards MA. DNA index, S-phase fraction, histological grade and prognosis in breast cancer. *Br J Cancer* (in press).

Law, politics, and the GPs' contract

GMSC won't break law but will identify contract defects

General practitioners throughout Britain are angry—with Mr Kenneth Clarke and with their leaders. A new contract that was rejected by a large majority in a national ballot of general practitioners has been imposed on them by the Secretary of State for Health.[1] He has acted within the law, and the General Medical Services Committee is to keep its opposition to the new contract within the law (p 1107). Doctors' anger is, however, qualified by the recognition by general practitioners that on this issue the public is confused and by no means totally supportive. Some of the changes in the new contract, such as making it easier for patients to change doctors and health checks for the elderly, seem good ideas to the average citizen. Last week the GMSC examined the law and the politics of the imposed contract and advised its angry constituents to be patient and not to embark on any sort of industrial action—it would only harm patients. So has Mr Clarke "won"? And what happens next?

General practitioners know but most of the public still seems unaware that this dispute predates the white paper *Working for Patients*.[2] The new general practitioner contract is based on an earlier white paper, *Promoting Better Health*, which appeared in 1987.[3] Confidential negotiations between the Department of Health and general practitioner leaders on the proposals for a new contract began even earlier than that and continued until May of this year, when the GMSC negotiators reluctantly agreed to commend to general practitioners a new form of contract as "the best they could achieve." At the time their chairman, Dr Michael Wilson, told Mr Clarke that it was by no means certain that general practitioners would agree to the deal. When they were consulted most of the general practitioners rejected the new contract; the secretary of state refused to reopen negotiations; and having "consulted" with the profession as the law requires, on 16 October he announced that he would be laying regulations on the contract before parliament this session and that it would come into force in April 1990.[4,1] With the government's large parliamentary majority there is little doubt that Mr Clarke will achieve this objective.

Why are general practitioners so angry? Firstly, they really do not like the new contract. They resent the secretary of state's negotiating tactics and having imposed on them substantial changes to their working conditions and the way they are paid. They resent the emphasis on numbers of patients and object to much of the detail such as the requirement to measure patients' heights, which is tantamount to clinical direction. Secondly, many general practitioners cannot understand why the GMSC is continuing to negotiate with the Department of Health about a contract that they have resoundingly rejected. As a result some seem to have lost faith in their negotiators—a feeling evidenced by a proposal of "no confidence" in Dr Wilson at the meeting of the GMSC last week, though the committee supported him by a vote of 47 to 19.

Mr Clarke's intransigence was signalled well ahead, and the BMA and the GMSC have had time to consider the choices available to them. The report of the alternative strategies working party (regrettably leaked to the Sunday press, in the fashion of the times) was discussed at length by the committee last week, but the conclusion was inevitable. Resignation from the NHS is the last resort, and it would succeed as a strategy only if most doctors would be willing to support the move. One suggestion, unilateral variation in the contract by doctors, would be illegal—and if organised by the BMA could lead to legal redress for incitement to breach of contract. In the world of industrial disputes as currently defined doctors have no practicable way of attacking their employer (strictly, the party to their contracts) without harming patients.

So the committee has recommended patience. It will continue its efforts to modify further the regulations—improvements have already been achieved. The contract and the regulations that will impose it will be "subjected to a careful scrutiny in order to provide the basis for a published report on the defects and the deficiencies resulting from the imposition."

This means, in effect, that general practitioners' representatives recognise that they have had to retreat after this battle but that they are not by any means defeated. Time is on the side of the medical profession. Governments come and go and so do health ministers: patients and doctors remain. Within two years this government will want to go into the next election campaign with some appearance of having solved the problems of the NHS. At this stage all it has managed is to antagonise most general practitioners, having already antagonised many hospital doctors, and the NHS review has yet to go through parliament.

We hope, however, that talk in the press of battles and victories can now be forgotten. Like the partners in a marriage (before the days of divorce) the doctors in the NHS and the government have got to go on working together; that means talking together and achieving some accommodation. Mr Clarke will recognise this, sooner or later.

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1 Anonymous. Mr Clarke claims contract is "good news for GPs." *Br Med J* 1989;**299**:1035.
2 Secretaries of State for Health, Wales, Northern Ireland, and Scotland. *Working for patients*. London: HMSO, 1989. (Cmnd 555.)
3 Secretaries of State for Social Services, Wales, Northern Ireland, and Scotland. *Promoting better health*. London: HMSO, 1987. (Cmnd 249.)
4 Macpherson G. Close vote and now a ballot on GPs' contract. *Br Med J* 1989;**299**:6.