MEDICAL PRACTICE

Occasional Review

Mammary cancers and pregnancy

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Uncertainties persist about management and prognosis of mammary cancers that occur during and after pregnancy and during lactation. Pathological features of mammary cancers occurring during pregnancy are the same as those in non-pregnant women and survival rates are comparable. Management should be the same as in non-pregnant patients. Termination of pregnancy does not improve survival but it should be advised if the prognosis is poor. Mastectomy apparently presents little danger to the fetus, though treatment such as chemotherapy and irradiation should be avoided. Women who have received treatment for mammary cancer need not be advised against subsequent pregnancy. Routine ovarian radiation in non-pregnant premenopausal women is not generally to be recommended, since it does not prolong survival and would deprive some of the chance of further pregnancy. In lactating women who develop mammary cancers survival is apparently not adversely affected. Lactation should be suppressed initially and followed by mastectomy. Regimens of immunotherapy, chemotherapy, or radiotherapy may then be begun.

Until results of current trials of combined treatments of mammary cancers associated with pregnancy are available, management should be neither aggressive nor tentative. It should be based on a well-balanced concept of applying all available treatments, as in non-pregnant patients.

Introduction

Any cancer or other potentially fatal disease in a young person is tragic, doubly so when the patient is a pregnant or lactating woman. Expected joy is turned to doom-laden pessimism for families, for young husbands, and for existing and expected children. Similar problems arise when a woman previously treated for mammary cancer becomes pregnant. Mammary cancers presenting during pregnancy or lactation are complex problems and concurrent pregnancy and subsequent pregnancy require separate consideration.

Concurrent pregnancy

Because the coincidence of these two events is low (about 1 in 3000 pregnancies,^{1,2} around 3% of all breast cancers) few large series have been available for study. Kilgore's description of 49 cases³ was the first to report on a series large enough to draw conclusions about prognosis and treatment; 70% of his patients without affected lymph nodes survived five years, and he emphasised that mastectomy should be performed and that the risks to the fetus were small. White⁴ reviewed 1375 cases and concluded that the outlook for pregnant women with mammary cancer was much the same as that for non-pregnant women. The view that the nature of the disease demanded either aggressive and indiscriminating management or a pessimistic attitude seemed to be unfounded. Poor results in isolated cases continue to promote pessimistic views, however, and the opening sentence of one influential statement⁵ on this subject is: "Carcinoma of the breast developing during pregnancy or lactation is a dread disease."

Haagensen and Stout⁶ studied 20 patients and concluded that a mammary cancer associated with pregnancy or lactation should not be treated by mastectomy. This view was subsequently retracted,^{7,8} but even today many allow their logical assessment of the prognosis to be obscured by their emotional responses towards cancer in the young. The necessarily limited experience of individuals has led to the appearance of many poorly substantiated statements and opinions similar to the example cited above, despite a few reports of several hundreds of patients⁹⁻¹¹ that confirm the views of Kilgore³ and White.⁴

Delay in diagnosis, as often due to the doctor as to the patient,^{12,13}

has been a persistent problem. Bunker and Peters¹³ found that only 7% of 150 patients were treated within one month of detection of the lump in the breast. Today greater alertness of both doctors and patients and more frequent use of fine-needle aspiration cytology should minimise this potential source of failure.

The pathological features of mammary cancers occurring during pregnancies are no different from those in non-pregnant women. The incidence of inflammatory cancers^{5 14 15} does not increase with pregnancy and lactation, as is often assumed, for they compose about 1.5% of all mammary cancers, and the average age of about 50 years is that of mammary cancers in general. In some series of pregnant patients the occurrence of metastases in axillary lymph nodes has been observed more often than is usual (table I). Haagensen⁵ describes certain microscopic features of grade I, intraductal, papillary, small-cell, and circumscribed cancers which carry a favourable prognosis, 15 out of 26 patients surviving 10 years, while only 16 out of 48 patients with grade II or III survived 10 years. Although the numbers are small, the observations are similar to those of mammary cancers in general described by Bloom and Richardson¹⁶ and Schiødt.¹⁷

Overall, survival is the same as in non-pregnant women (figure).¹⁰ Some^{4 11} have regarded survival in those with axillary nodal metastases as poorer than in comparable non-pregnant patients, but Peters¹⁰ found that this apparent difference in crude data was reduced to insignificant levels when patients were matched for age as well as stage. Patients under 30 had a poorer outlook than others (table II), and the

TABLE I—Incidence of histological axillary lymph-nodal metastases in mammary cancers detected during pregnancy or lactation as reported in various series

Series	Total	No (%) with nodal metastases
Peters and Meakin ⁴	187	140 (75)
Holleb and Farrow ⁹	133	96 (72)
Montgomery ⁵	70	52 (74)
Haagensen ⁵	41	31 (76)
White and White ¹⁷	25	18 (72)
Harrington ¹⁸	92	78 (85)
Totals	548	415 (76)

TABLE II—Age-related survival in 187 patients five years after diagnosis of breast cancer during pregnancy*

Age (years):	<30	31-35	36-40	>40
Survival rate (%)	26	34	45	30

*Adapted from Peters.¹⁰

Survival curves for 221 pregnant or lactating patients (solid line) and 221 non-pregnant patients (broken line) with mammary cancers who were matched for age and tumour stage. X=Those with mammary cancer in first half of pregnancy who survived five years after treatment. O=Those with mammary cancer in second half of pregnancy who survived five years after treatment. Adapted from Peters.¹⁰

five-year survival of patients treated in the second half of pregnancy was only 11% compared with 48% for those treated in the first half (figure). Seven out of nine comparable patients treated in the early postpartum phase survived beyond five years. Pessimism about mammary cancers associated with pregnancy apparently stemmed from experience with cancers in the later months of pregnancy.

Management

The general approach to management should be the same as in non-pregnant patients. Termination of the pregnancy has not been shown to improve survival and should not be advised routinely, but the wishes of the patient and her husband must be carefully considered. If an additional dependant would overtax family resources should the mother fail to survive for a decade or so, then termination might be the sensible course of action, after due consideration of the age of the fetus and of the ages and religious and mental attitudes of the parents. Termination might be more strongly advised because of the poor outlook for the patient in the presence of the following poor prognostic features: oedema or ulceration of the skin; solid fixation of the primary tumour to the chest wall; an axillary nodal mass 3 cm or more in diameter or attached to skin or deep tissues; and four or more axillary nodes harbouring metastases (in this case pregnancy would need to be terminated after histological examination of the tissues excised at mastectomy and axillary clearance).

Some have favoured termination on the basis of brief reports or isolated catastrophes in their own experience.^{2 5 18} The data available from the large series of Peters¹⁰ and of Rosemond and Maier¹¹ show that termination of the pregnancy has no obvious beneficial effect on the survival of patients who are pregnant when the mammary cancer is discovered, and it seems unlikely that metastases will lodge in the fetus.¹⁹ Although cells of maternal melanoma²⁰⁻²⁶ lymphosarcoma,²⁷ and leukaemia²⁸ have been described in fetuses, such a potentially lethal transplacental traffic seems to be surprisingly small in relation to the rate of concurrence of pregnancy with cancers.

If termination is not desired treatment that might damage the fetus should be avoided. Operations such as mastectomy apparently present little danger to the fetus. Radiation undoubtedly damages fetal tissues and there is controversy about whether any minimal permissible dose of radiation to the fetus exists. Abnormally small head circumference and mental retardation were observed in children after intrauterine radiation of as little as 10-19 rads before the 18th week of gestation in Hiroshima. In Nagasaki no effect was observed under 150 rads.²⁹ With a total therapeutic dose of 7500 rads the lowest dose calculated to be received by an early fetus 25 cm below the base of a radiation field for mammary cancer is 30 rads.³⁰ Hence radiotherapy in the first half of pregnancy seems to be contraindicated. Though the risk of teratogenesis is slight during the second half of pregnancy, the fetus is larger and will receive more radiation with a considerable risk of leukaemogenesis and carcinogenesis. Most chemotherapeutic drugs are teratogenic, and must constitute a high risk to the fetus at any stage of gestation.

When delivery is expected or planned within a few weeks it is reasonable to delay all treatment until two weeks after parturition, while lactation is suppressed with bromocriptine 2.5 mg taken with food on the day of delivery, followed by 2.5 mg twice daily for 14 days. Postponement of treatment may avoid the dangers in the latter half of pregnancy described by Peters.¹⁰ Mastectomy can then be performed and the following guidelines pursued.

(1) GENERAL CONSIDERATIONS

The risks of cancer to the mother and those of treatment to the fetus must be established by comprehensive clinical and laboratory investigations and personal assessments. Interdisciplinary consultation is needed and the surgeon should discuss the risks with experienced colleagues in obstetrics and radiotherapeutics. Problems of management should be discussed frankly with the patient and her husband, and they should be told of the main possibilities. These are generally mastectomy only and continuation of the pregnancy if desired when prognostic features are good, or mastectomy plus chemotherapy or radiotherapy with serious consideration of termination of the pregnancy when prognostic features are poor. If the parents reject the advice initially a compromise management with least harm to the mother and fetus must be devised to suit each case. Some of the most crucial decisions affecting management must be made by the mother and her husband, and the surgeon must remain neutral in these

discussions and restrict positive comments to the strictly medical problems.

(2) STAGE I OR II TUMOURS

(a) If no metastases are present in axillary nodes no further active measures are required. Three-quarters of such patients can be expected to survive five years and further pregnancies should not be discouraged (see below).

(b) With axillary nodal metastases intermittent oral chemotherapy regimens similar to those described by Fisher *et al*³¹ and Bonnadonna *et al*³² can be expected to prolong freedom from recurrence and possibly survival. Combined treatment with cyclophosphamide, methotrexate, and fluorouracil³² carries considerable risks of undesirable side effects, such as alopecia, leucopenia, and cystitis. We favour replacing cyclophosphamide with phenylalanine mustard in this combination and giving fluorouracil by mouth. This is an easily controlled, wholly oral, and less toxic combination taken in five-day schedules every six weeks for one or two years after mastectomy or parturition, whichever is later.

(c) When the risk of local implantation or recurrence is high, as with large cancers in small breasts or cancers close to the circumference of the breast, postoperative radiotherapy to the skin flaps will reduce the incidence of this complication. Simultaneous irradiation of the lymph drainage areas may help to control metastases, but may be harmful to those with no metastases in the axillary lymph nodes.^{33 34} The possibility of increasing the radiosensitivity of residual cancer and of producing systemic immunity with the immunotherapeutic regimens described by Anderson *et al*³⁵⁻³⁹ and Rojas *et al*⁴⁰ should also be considered as they were closely controlled studies in centres with appropriate experience.

(3) STAGE III OR IV TUMOURS

Termination of pregnancy should be strongly advised. Irradiation of stage III cancers followed by levamisole, 50 mg thrice daily on three occasions weekly for six months, can reduce large cancers and axillary metastases, making subsequent mastectomy and axillary clearance easier and reducing the chances of cancer implantation and local recurrence. Even if local surgery is not feasible this management may prolong survival.⁴⁰ When distant metastases (stage IV) are present the pregnancy should be terminated by abdominal hysterotomy and oophorectomy performed at the same operation, followed by treatment with androgens in the form of depot testosterone, intramuscular nandrolone decanoate (Deca-Durabolin), or oral fluoxymesterone. Control of failures or subsequent recurrences may be achieved for short periods with one of the high-dose polychemotherapy regimens currently advocated⁴¹⁻⁴³ for comparable non-pregnant patients.

Contraception—After initially successful treatment contraception should be mechanical. Effects of long-term ingestion of oestrogens and progestogens on micrometastases from mammary cancers are unknown.

Pregnancy after cancer

Many have observed apparently improved survival in patients who become pregnant after treatment for mammary cancers. One theory is that the patients are a selected population after early death of those with aggressive cancers. Nevertheless, Peters¹⁰ found in a carefully controlled series of 96 subjects matched for age and tumour stage with non-pregnant patients that the rate of survival for up to 10 years was higher in the pregnant patients. This difference persisted throughout a range of pregnancies occurring within six months of the cancer to those occurring two years or more after the cancer. Hence it did not seem to be due to early death of those with aggressive cancers, and pregnancy may even prolong life in some patients, especially those under 35.

We may therefore conclude that patients need not be advised against pregnancy as a hazard to their longer survival, and they may be encouraged if familial and social factors support the addition of another dependant who, it is understood, may lose his or her mother at an early age. Routine ovarian radiation for all premenopausal patients, which is advocated in some centres,⁴⁴ is not generally recommended, since it would deprive some of the possible benefits of subsequent pregnancy and, although it may prolong the disease-free interval, it does not prolong survival.

Lactation

The only long-term follow-up study of patients developing mammary cancers during lactation is that of Peters.¹⁰ Out of 39 patients, about a half were alive after 10 years, but full details are not given. This observation and those from other studies, in which lactating patients were grouped with pregnant patients, show no obvious effects upon survival.

Lactation should be suppressed with bromocriptine for at least one week to allow the size and vascularity of the breast to diminish. Then mastectomy plus axillary sampling or clearance may be followed by a regimen of chemotherapy, immunotherapy, or radiotherapy, whichever is judged to be appropriate for the individual patient according to the guidelines for management described above.

Conclusion

Management of mammary cancers and other common cancers that are generally treated by some form of surgical excision is uncertain at present. The deficiencies and the advantages of long-established concepts have been more clearly defined by surgeons in recent years and we live in a period when systemic controls of malignant growth seem to be evolving. Although the approaches to chemotherapy and immunotherapy advocated above will find both supporters and opponents, the many current trials of combined treatments will undoubtedly provide information to aid in stratifying patients with mammary cancer into subpopulations with clearly defined responses to different treatments, whether endocrine, lymphoreticular, or chemotherapeutic; until then major uncertainties will persist.

The interrelations between mammary cancers and pregnancy and lactation described above, and their relation to patient care and recent epidemiological⁴⁵ evidence of protection by early pregnancy should take an important place in our increasing comprehension of endocrinological controls of mammary cancers. Meanwhile, the management of cancers associated with pregnancy should be neither aggressive nor tentative. Although a four-pronged onslaught of mastectomy, termination of pregnancy, sterilisation, and radiotherapy may be indicated in a few cases it is unsympathetic and unlikely to benefit a young woman with a small chance of a lengthy life. On the other hand, mastectomy alone is occasionally adequate but other treatments should always be thoroughly considered. It is important to retain a well-balanced concept of the application of all available treatments that is based on the principles that guide our care of the non-pregnant patient.

References

- White, T T, *Surgery, Gynecology and Obstetrics*, 1955, **100**, 661.
- Montgomery, T L, *American Journal of Obstetrics and Gynecology*, 1961, **81**, 926.
- Kilgore, A R, *Archives of Surgery*, 1929, **18**, 2079.
- White, T T, *American Journal of Obstetrics and Gynecology*, 1955, **69**, 1277.
- Haagensen, C D, *Diseases of the Breast*, 2nd edn. Philadelphia, Saunders, 1971.
- Haagensen, C D, and Stout, A P, *Annals of Surgery*, 1943, **118**, 859.
- Haagensen, C D, *Diseases of the Breast*, 1st edn. Philadelphia, Saunders, 1956.
- Haagensen, C D, *American Journal of Obstetrics and Gynecology*, 1967, **98**, 141.
- Holleb, A I, and Farrow, J H, *Acta Unionis Internationalis Contra Cancrum*, 1964, **20**, 1480.
- Peters, M V, in *Prognostic Factors in Breast Cancer*, ed A P M Forrest and P B Kunkler, p 65. Edinburgh, Livingstone, 1968.
- Rosemond, G P, and Maier, W P, in *Breast Cancer: Early and Late*, p 227. Chicago, Year Book Medical Publishers, 1970.
- Westberg, S V, *Acta Obstetrica et Gynecologica Scandinavica*, 1946, **25**, suppl No 4.
- Bunker, M L, and Peters, M V, *American Journal of Obstetrics and Gynecology*, 1963, **85**, 312.
- Lee, B J, and Tannenbaum, N E, *Surgery, Gynecology and Obstetrics*, 1924, **39**, 580.
- Taylor, G W, and Meltzer, A, *American Journal of Cancer*, 1938, **33**, 33.
- Bloom, H J G, and Richardson, W W, *British Journal of Cancer*, 1957, **11**, 359.

- ¹⁷ Schiødt, T, *Breast Carcinoma. A Histologic and Prognostic Study of 640 Followed-up Cases*. Copenhagen, Munksgaard, 1966.
- ¹⁸ Cade, S, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1964, **71**, 341.
- ¹⁹ Anderson, J M, *Nature's Transplant. The Transplantation Immunology of Viviparity*, p 36. London, Butterworths, 1972.
- ²⁰ Friedreich, N, *Virchows Archiv für pathologische Anatomie und Physiologie und für Klinische Medizin*, 1862, **36**, 465.
- ²¹ Gottron, H, and Gertler, W, *Archives of Dermatology and Syphilology*, 1940, **181**, 91.
- ²² Holland, E, *Journal of Obstetrics and Gynaecology of the British Empire*, 1949, **56**, 529.
- ²³ Dargeon, H W, Eversole, J W, and Delduca, V, *Cancer*, 1950, **3**, 299.
- ²⁴ Cavell, B, *Acta paediatrica*, 1963, suppl No 146, p 37.
- ²⁵ Aronson, S, *Acta paediatrica*, 1963, **52**, 123.
- ²⁶ Brodsky, I, et al, *Cancer*, 1965, **18**, 1048.
- ²⁷ Berghinz, G, *Gazzetta degli ospedali di Milano*, 1900, **21**, 606.
- ²⁸ Rigby, P G, Hanson, T A, and Smith, R S, *New England Journal of Medicine*, 1964, **271**, 124.
- ²⁹ Miller, R W, and Blot, W J, *Lancet*, 1972, **2**, 784.
- ³⁰ Denoix, P, *Recent Results in Cancer Research*, 1970, **31**, 83.
- ³¹ Fisher, B, et al, *New England Journal of Medicine*, 1975, **292**, 117.
- ³² Bonadonna, G, et al, *New England Journal of Medicine*, 1976, **294**, 405.
- ³³ Paterson, R, and Russell, M H, *Journal of the Faculty of Radiologists*, 1959, **10**, 175.
- ³⁴ Bond, W H, in *The Treatment of Carcinoma of the Breast*, ed A S Jarrett, p 24. Amsterdam, Excerpta Medica, 1967.
- ³⁵ Anderson, J M, et al, *British Journal of Surgery*, 1970, **57**, 557.
- ³⁶ Anderson, J M, et al, *British Journal of Cancer*, 1973, **28**, suppl No 1, p 83.
- ³⁷ Anderson, J M, et al, *British Journal of Surgery*, 1974, **61**, 778.
- ³⁸ Anderson, J M, et al, *Cancer*, 1977, **40**, 30.
- ³⁹ Anderson, J M, Kelly, F, and Gettinby, G, *Developments in Biological Standardisation*, 1978, **38**, 433.
- ⁴⁰ Rojas, A F, et al, *Lancet*, 1976, **1**, 211.
- ⁴¹ Carter, S K, *Cancer*, 1972, **30**, 1543.
- ⁴² Carter, S K, *Cancer Treatment Reviews*, 1976, **3**, 141.
- ⁴³ Brown, I, and Ward, H W C, *Clinical Oncology*, 1976, **2**, 105.
- ⁴⁴ Ribeiro, G G, and Palmer, M K, *British Medical Journal*, 1977, **2**, 1524.
- ⁴⁵ McMahon, B, et al, *Bulletin of the World Health Organization*, 1970, **42**, 185.
- ⁴⁶ Peters, M V, and Meakin, J W, *Progress in Clinical Cancer*, 1965, **1**, 471.
- ⁴⁷ White, T T, and White, W C, *Annals of Surgery*, 1956, **144**, 384.
- ⁴⁸ Harrington, S W, *Annals of Surgery*, 1937, **106**, 690.

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STRANGE ENCOUNTERS

MD oral

As usual, three examiners had been appointed to assess the thesis submitted by a candidate for the MD. Two were nominated because of their knowledge of the subject of the thesis; the third, the chairman, represented the examining board of the university. Although they were well satisfied by the standard of the thesis, the two "experts" thought it desirable to have an opportunity to discuss a few points with the candidate so that these might be clarified.

As is customary in such circumstances, the experts sent a summary of their assessment to the chairman of the examination, explaining why they wanted to meet the candidate and asking that an oral examination should be arranged. The chairman's secretary replied for him, stating that he considered an oral examination to be unnecessary as, in his estimation, the thesis was quite acceptable. She hoped that they would not press for a meeting with the candidate as the chairman was a very busy gentleman. The experts tried to telephone their chairman, failed, and therefore wrote to him again. The secretary fixed an appointment for the examination: it would take place in the chairman's consulting rooms at 4 o'clock, sharp, on a day two months ahead—the earliest date he could manage without inconvenience.

The busy man was not in when the other examiners got to his rooms a little before the appointed hour on the afternoon of the examination. His secretary told them to wait with the candidate in the hall, where there were two chairs (the waiting room was reserved for patients). It was 4.45 when the chairman arrived. He went directly to his consulting room, without glancing at the three men standing in the hall. He saw a couple of patients and then, at about 5.30, sent his secretary to bring in his co-examiners and the candidate, and to tell them that they were not to smoke in his room. All three were non-smokers. To the secretary's annoyance, the two examiners asked the candidate to wait a little longer as they had to have some discussion with the chairman about the thesis.

The chairman greeted his colleagues with a simple "Good day." He did not stand up or shake hands. He did not refer to the delay but at once began the business of the occasion. "Calling this fellow for a viva voce is just a formality," he said, "he has written a long thesis and must have spent some time on it. I have looked through most of it and what I have seen is satisfactory. There are no questions that need to be put to him. I expect you agree with me."

The other examiners pointed out that the meeting was taking place because there were questions that they needed to put to the candidate. The busy man was annoyed. "As you wish," he said, "but we shall be brief—I have an engagement at half past six. You have 25 minutes, no more." He rang a bell. The secretary came in. "Tea," he said, without looking up. She returned immediately, with her assistant. The assistant carried a tea tray to the chairman's desk. The secretary poured a cup, added sugar, stirred it, and laid a slice of lemon carefully on the surface of the brew. She set the cup within convenient reach of his hand. He ignored her but lifted the cup and sipped noisily at its steaming contents. She bowed slightly and left. There was only one cup. Meantime, the two visitors had helped themselves to seats; it was evident that no one else would look to their comfort.

The chairman signed a few letters and then used the house telephone to order some one to bring the car round in a quarter of an hour: he would be ready to leave then, he said. It was a quarter-to-six. He rang for his secretary and told her to bring the candidate in. He was charming to the young man, shaking hands at length, pulling up a chair for him, and congratulating him on his thesis. "This viva voce is just a formality," he said, "quite unnecessary in my opinion, but these professors seem to have one or two small points that they feel they must put to us to justify the occasion. Then it will all be over and you will be looking forward to meeting the chancellor of the university on graduation day. I am only sorry that it was so difficult to find a day suitable to the examiners—they are very busy men, you know, but I had hoped we might have completed this some weeks ago and then you would have graduated at next month's ceremony instead of having to wait an extra six months. My warmest congratulations. An outstanding thesis. One of the longest I have read. Splendid, indeed, quite splendid!"

The candidate dealt clearly and concisely with the points that the experts had wanted to discuss with him. At six o'clock he was ushered out by the chairman, who gave him no opportunity to say goodbye to the other examiners or even to shake hands with them. The chairman did not return. His secretary conducted the others back to the hall, seemingly as oblivious to the seething of the younger examiner as to the unsurprised resignation of the older man. She told them to wait while she completed the examination documents, explaining that the chairman had told her what to write about the thesis and had signed the appropriate report forms, knowing, as she said, that she would make no mistakes.

What she typed was in fact acceptable to the experts, and they added their signatures. Their consciences were clear. Presumably so was the chairman's. To his surprise, for I have heard him remark on it, he was never again asked to take the chair at an MD oral during the rest of his term as a member of the examining board.

Gentleman's word

Once upon a time I was upbraided by my boss when, not long after taking up a new job, I had had occasion for the first time to make an administrative decision that, or so I thought, required to be expressed in writing. It was a trivial matter, relating to the institution's arrangements for essential work in its departments to continue over a holiday period. My letter simply confirmed that the arrangements proposed were suitable for the needs of the department to which I was attached. The head of the department, telling me that I ought not to have acknowledged the administrator's letter, said, "Never acknowledge anything in writing, or verbally if what you say might be taped: for, believe me, if you do, you will not afterwards be able to deny receiving it."

There are such people still, and they are still liable to be found at any level in any organisation, and surely only to its detriment.—WILL MACREDIE.