another example of high antibody content of foetal blood, and in this respect confirms the previous findings. A striking feature of the results is the consistent relationship between the mother's and the infant's antibody level as well as the magnitude of the latter.

The significance of these findings, and the revised view of placental permeability to antibodies to which they lead, was discussed in a previous paper (Calman and Murray, 1951). In that paper we concluded that the simple filtration hypothesis was becoming untenable, and our present results support that opinion.

Summary

In 46 cases the anti-streptolysin O titre of the maternal and cord blood was estimated at the time of delivery. The level in the cord was at least twice that of the mother's in 33 cases; it was higher in 41 cases, about the same in three, and lower in only one. In one case both levels were too low to be measured.

The material for investigation was obtained through the co-operation of the obstetricians, paediatricians, and labour ward staff of Queen Charlotte's Maternity Hospital.

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NATURAL HISTORY OF CYSTIC DISEASE OF BREAST TREATED CONSERVATIVELY

BY

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Cystic disease of the breast is a common and clearly defined clinical entity. Though it has been known since the time of Réclus that the condition is potentially multiple and bilateral, much the commonest manifestation clinically is as a solitary lump in one breast, the breasts otherwise being clinically normal. If the fluid from this solitary lump is aspirated, the affected breast, after a few hours in which the site of the aspirated cyst may be felt as a hollow, becomes normal to inspection and palpation. Cystic disease of the breast has sometimes been regarded as a potentially dangerous condition with an increased liability to the development of carcinoma. The support for this view is derived less from clinical evidence than from indirect evidence in the form of histological (Cheatle, 1934-5; Willis, 1948) and animal experimental findings (Cheatle, 1934-5).

The acceptance of the view that cystic disease of the breast is a dangerous condition naturally leads to some type of excision, often simple mastectomy. While this procedure averts the postulated danger in the affected breast, it is often at the price, from the human standpoint, of a serious mutilation of the patient's womanhood, and, from the scientific standpoint, of the destruction of the clinical evidence of the subsequent

natural course of the disease, which might have been innocent. Moreover, it is irrational to do a unilateral extirpation for a bilateral disease.

During the twenty-odd years that one of us (D. H. P.) has been in consultant practice he has consistently regarded cystic disease of the breast as essentially an innocent condition, to be treated preferably by aspiration. There has been one important exception to this conservative attitude. If there was any suspicion of intracystic growth—and this is easily determined if a few simple rules which will be mentioned later are followed—the condition was explored at operation and treated accordingly. The number of these cases was small, and in all of them the growth was present at the time that the patient first presented herself; in no case did it develop as a late complication in a simple cyst treated primarily by aspiration. It is argued later that these facts may warrant these cases with intracystic growth being placed in a separate group, not only from the point of view of practical management but also pathologically; and that in many cases the cyst may be a response to the growth rather than the growth being a complication of the cyst. Apart from evidence of growth in a cyst, the presence of any pathological solid lump in a breast which also contained a cyst was regarded as an indication for exploration and biopsy, as in a breast without a cyst.

In this paper the results of the above-defined conservative attitude to simple cystic disease of the breast are given. A detailed analysis can be made only of cases of cysts seen in private, because the much larger hospital group were treated as out-patients, and their records are buried in an unindexed mass of out-patient material. An attempt has been made to get over this difficulty to some extent by analysing in-patient hospital records of cases of carcinoma of the breast from the point of view of a previous history of cystic disease. The small number of cases of cystic disease with evidence of simultaneous intracystic growth are analysed separately.

Analysis of Results

Table I analyses all breast cases seen in private practice to show the relative frequency of cystic disease. The table almost certainly does not represent the true relative incidence

TABLE I.—*Diagnosis in 535 Consecutive Breast Cases Seen During 1931-50 (D. H. P.)*

Carcinoma of breast (including 5 cases of Paget's carcinoma) ..	260 cases
Painful breasts	102 "
Cysts of breast	76 "
Fibroadenoma	28 "
Abscess	25 "
Discharge from nipple	19 "
Miscellaneous	25 "

of breast conditions, owing to the unconscious selection imposed by private consultant practice. For example, painful breasts and fibroadenomata are probably much commoner than indicated, as also is the more recently defined entity known as periductal mastitis (Geschickter, 1943), or duct stagnation (Patey, 1949). But since carcinoma of the breast and cystic disease both present in a similar age group with the same symptom of a painless lump, the relative incidence of cases of carcinoma and cyst can probably be regarded as approximately accurate—that is, seven cases of carcinoma to two of cyst. It will be noted that no case has been diagnosed as chronic mastitis, which has been regarded as a non-existent disease (Patey, 1951), the postulated existence of which under this or any other name has befogged breast pathology and diagnosis for far too long.

In all 76 cases of cyst the diagnosis was proved—in 69 by aspiration and in 7 by operation. Operation was performed either because aspiration had failed, the cyst being

missed or aggregated small cysts too small to aspirate being present, or with the mistaken diagnosis of a solid lump. In all seven cases operated on, only a local excision of the cyst was carried out.

Of the 65 cases traced, to date 64 have not developed carcinoma, and one has developed carcinoma in the opposite breast. Table II gives details of these cases. The 64 cases

TABLE II.—*Follow-up of Cases of Cyst Treated by Tapping from Point of View of Development of Carcinoma*

No Carcinoma Developed After: Years	Cases	No Carcinoma Developed After: Years	Cases
16	3	7	2
15	2	6	7
14	3	5	6
13	1	4	7
12	1	3	8
11	0	2	8
10	2	1	8
9	3		
8	3		
			64

Carcinoma developed in opposite breast in three years in 1 case. Untraced—11 cases.

free of carcinoma have been followed up for periods varying from 1 to 16 years. The one case that developed carcinoma did so in the opposite breast three years after aspiration of a simple cyst in the first breast.

Table III gives the after-history from the point of view of the development of further cysts. It will be seen that of 55 cases treated two or more years previously on which

TABLE III.—*Follow-up of Cases of Cyst Treated by Tapping from Point of View of Recurrence of Cyst*

Total cases treated by aspiration 2 or more years ago ..	55 cases
Further cysts	20
No further cysts	35
—after 2 years in 5 cases	
" 3 " " 6 "	
" 4 " " 4 "	
" 5 " " 3 "	
" 6 " " 6 "	
" 7 " " 1 case	
" 8 " " 1 "	
—after 9 years in 1 case	
" 10 " " 1 "	
" 12 " " 1 "	
" 13 " " 1 "	
" 14 " " 2 cases	
" 15 " " 1 case	
" 16 " " 2 cases	

information is available on this point, 35 have not developed further cysts and 20 have. Of the 35 cases that have not, the time that has elapsed varies from 2 to 16 years. Of the 20 cases that have developed further cysts, in 13 the further cyst or cysts were in the same breast, in two in the opposite breast, and in five in both breasts. Some further points of interest not brought out in the table may be mentioned. The first is that regular recurrences of cysts may be followed by apparent abatement. Thus, a patient had a cyst aspirated in 1942, another in the opposite breast later in the same year, and another in the first breast in 1943. From then up till the time of follow-up (1951) she had had no further trouble. Again, a patient had cysts aspirated in 1942, 1944, 1946, and 1947. From then till 1951 she had no further trouble. Secondly, large cysts do not seem particularly prone to recurrence. Thus one patient with a cyst from which 70 ml. had been aspirated had had no recurrence six years later, and another with a 120-ml. aspiration was well five years later without recurrence. One of the patients with the longest follow-up of 16 years with no recurrence of cysts had 23 ml. aspirated.

One may conclude, therefore, that, judged by the current experience over 20 years of a surgeon whose normal practice is to treat cysts of the breast by aspiration, either there is no special tendency to carcinoma or, if there is such a tendency, it requires a longer period of observation to elicit it. In the only case in which so far carcinoma has developed, since it occurred in the opposite breast to the cyst, only routine bilateral mastectomy would have prevented it; and such a drastic prophylactic procedure would require strong evidence for its justification. Apart from the question of carcinoma, the present study shows that the tendency to the development of cysts often dies out, sometimes after only one manifest cyst, at other times after a succession of cysts. Conservative treatment by aspiration is thus only a minor and often temporary burden for the patient.

The results of an analysis of the histories of 810 cases of carcinoma of the breast seen during the years 1930–50 from the point of view of a history of previous cysts are given in Table IV. These include all cases of carcinoma

TABLE IV.—*Analysis of 810 Cases of Carcinoma of Breast from Point of View of Previous Clinical History of Cysts (1930–50)*

No previous history of cyst	800
Previous history of cyst	10
(a) In 5 cases carcinoma in same breast as previous cyst	
(b) In 3 cases carcinoma in opposite breast to previous cyst	
(c) In 1 case carcinoma and cystic disease bilateral	
(d) In 1 case carcinoma unilateral and cystic disease bilateral	

Cases in which the history was of the previous removal of a lump which may have been a cyst, but in which the diagnosis was not definite, have for the purpose of this table been included in the 10 positive cases.

of the breast seen by one of us (D. H. P.) both in private practice and at the Middlesex Hospital during these years. It also includes cases of carcinoma of the breast admitted to hospital from 1930 to 1939 under a late senior colleague, Mr. Eric Pearce-Gould, who used to treat as in-patients many of the breast cases seen by one of us as out-patients, and who also was in the habit of treating simple cysts of the breast by aspiration. It will be seen from Table IV that most cases of carcinoma of the breast gave no history of previous clinical cystic disease. In the minority that did give such a history the carcinoma was only slightly more common in the breast that had been the site of the cyst clinically than in the opposite breast (5:3). Even allowing for the possibility that in some cases the history of previous aspiration was not noted, it seems clear that such a history is exceedingly rare. It can thus be concluded that, if carcinoma developed in cases of cystic disease treated conservatively as out-patients at Middlesex Hospital, the patients must have presented themselves almost exclusively to other hospitals for its treatment; and this seems a less likely conclusion than that the incidence of carcinoma was very small.

Cysts with Intracystic Tumour

As already noted, cysts with evidence of intracystic tumour have been regarded as possibly malignant and been operatively explored. Of the 886 breast cases analysed in this paper (76 cysts and 810 carcinomata) there were eight cases of cysts associated with intracystic growth (Table V).

TABLE V.—*Summary of Eight Cases Showing Carcinoma at Operation in Relation to a Cyst*

4 in association with intracystic papilloma
1 in association with aggregated multilocular cysts with intracystic papillomata
1 in wall of smooth-walled cyst
1 intracystic ?fibrosarcoma ?undifferentiated carcinoma
1 Paget's disease in opposite breast after previous mastectomy for simple intracystic papilloma in first breast

The presence of tumour in a cyst showed itself clinically in various ways. Sometimes, as in two of the eight cases, it was the tumour which was diagnosed clinically, not the cyst, the latter being noted only after amputation. In several there was a clinical history of blood-stained discharge from the nipple. But if the clinical diagnosis appeared to be simple cyst there were three features which were regarded as suspicious of intracystic tumour on aspiration and therefore warranting surgical exploration of the lump. The first was blood in the aspirated fluid, the second a persistent residual lump after aspiration, and the third a rapid—that is, within a few weeks—refilling of the cyst. We do not feel that the existence of this small and easily diagnosed group of cases of growth within a cyst of the breast ought to be allowed to prejudice the demonstrated efficiency of conservative treatment of simple cystic disease of the breast. We have recently begun the practice of getting the aspirated fluid from cysts centrifuged and examined for tumour cells, and this test should still further reduce the rare possibility of an intracystic carcinoma being missed.

Discussion and Conclusions

This paper is concerned with the natural history of cystic disease of the breast as based on clinical evidence. This does not imply any belittlement of other types of breast

study throwing light on the question, in particular histology. But, as already noted, histological evidence is often associated with an interruption of the natural history of cystic disease by a mastectomy or partial mastectomy. Only clinical evidence can be conclusive for the natural history of cystic disease of the breast as it affects the human, and it is precisely clinical evidence that has been lacking. The present paper again illustrates the time required and the difficulty experienced in obtaining conclusive clinical evidence, and it may be that a current experience of 20 years is too short a time for final conclusions. But one certainly seems justified on such current experience in tentatively concluding that, with certain simple precautions, the regarding and treating of cystic disease of the breast as an innocent condition has not up to the present been shown to be fallacious by the frequency of development of carcinoma.

The criticism might possibly be made that, from the point of view of the liability of cystic disease to carcinoma, the eight cases with associated intracystic growth ought not to be treated as a separate group, but ought to be grouped with the one case of cystic disease treated by aspiration in which subsequent carcinoma did develop. But in reply it should be emphasized that in all these eight cases it was not a question of a tumour developing as a complication in a previously known cyst treated conservatively, but of eight patients who at their first attendance had tumours of the breast which happened to be associated with cysts, often not diagnosed clinically. There was no definite evidence in any of them that the cysts preceded the tumours, and in most it was at any rate equally probable that the reverse process occurred and that the tumours preceded the cysts. Certainly in the commonest group—the intracystic papillomata (five cases)—the cysts were probably due to distension of the associated duct with the blood shed by the papillomata, a process that in lesser degree is recognized as a common occurrence in the small intraduct papillomata in the ducts near the nipple.

We feel, therefore, that many of these cases belong to a separate group pathologically as well as being clearly recognizable as a separate entity clinically, and that part of the confusion in the past about the relation of cystic disease of the breast to carcinoma has arisen through wrongly grouping together two separate types of condition. Finally, since carcinoma and cystic disease are both common conditions, it must occasionally happen that the two will present clinically at the same time. The treatment of these cases is of course the treatment of the carcinoma, but it would be wrong to assume from simultaneous presentation a necessarily causal relation between the two conditions. This study therefore furnishes support for the view that cystic disease of the breast can with simple precautions be treated conservatively. It also furnishes support for the efficacy of the simplest form of conservative treatment—aspiration.

Summary

Of 76 cases of cyst of the breast treated conservatively, 65 of which have been followed for from 1 to 16 years, only one is known to have developed carcinoma, and that in the opposite breast.

Aspiration of a cyst is not necessarily followed by the development of further cysts, and, if it is, the tendency to cyst formation may disappear.

Of 810 cases of carcinoma of the breast only 10 had a previous clinical history of cyst.

In a further eight of these cases growth developed apparently simultaneously with and in relation to a cyst, but this group of cases readily lends itself to recognition clinically, and is probably a separate group pathologically.

With simple precautions, conservative treatment by aspiration is an efficient and safe treatment for cystic disease of the breast.

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A.C.T.H. IN DIAGNOSIS OF ADRENAL INSUFFICIENCY (THORN TEST)

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In 1948 Forsham *et al.* investigated the metabolic and haematological response of human subjects to a single dose of 25 mg. A.C.T.H. They compared the response of 30 patients with Addison's disease with that of 10 normal subjects and 40 hospital patients with presumably intact adrenal cortical function. They found a mean fall of 74% in the number of circulating eosinophils in the individuals with normal adrenal cortical function, and a mean fall of only 4% in the patients with Addison's disease.

The fall in the eosinophil count was accompanied by a mean increase in the urinary uric-acid/creatinine ratio of 87% in the control series and of only 16% in the cases of Addison's disease. Both changes were maximal four hours after the injection of A.C.T.H. A normal eosinophil response, and at the same time an increase of 48% in the uric-acid/creatinine ratio, could, however, be elicited in patients with Addison's disease after they were given 20 mg. of 17-hydroxycorticosterone (compound F), suggesting that the response to A.C.T.H. was mediated by an increase in secretion of 11-oxy-steroid compounds by the adrenal cortex. On the basis of these observations Forsham *et al.* devised a "four-hour test" of adrenal cortical function.

In a later article Thorn *et al.* (1951) reported a larger series of similar observations. In 50 cases of Addison's disease there was an average fall of only 7% in the eosinophil count, and in about one-third of the cases there was actually an increase. Patients with hypopituitarism showed an average fall of 31%, the magnitude of the change depending upon the degree and duration of adrenal cortical involution.

Thorn and his colleagues also introduced a 48-hour test, in which changes in the eosinophil count and in the urinary 17-ketosteroid excretion were measured, in response to the intramuscular administration of A.C.T.H. in divided doses over a period of 48 hours (Thorn and Forsham, 1949; Roche, Forsham, Forsham, and Thorn, 1950; Thorn *et al.*, 1951). This test was carried out in 100 subjects. In 35 patients with normal adrenal cortical function the eosinophil count fell by 77% after 48 hours; the urinary 17-ketosteroid excretion increased by an average of 10.1 mg. per 24 hours in 15 normal male subjects and of 7.2 mg. per 24 hours in 20 normal female subjects, whereas there was no significant change in patients with Addison's disease. In most cases of hypo-