aid in differentiating this disease from cancer is to recognize the acute onset and subsequent clinical course. In plasma-cell mastitis the initial picture is that of an acute or subacute inflammation which appears suddenly and subsides rapidly. The process regresses steadily, whereas in carcinoma the process is reversed. The disease begins locally and extends progressively. A single examination is generally inadequate, for only by several examinations can one determine whether the disease is progressing or regressing. This is the most important single factor in the differential diagnosis.

Plasma-cell mastitis has to be distinguished from (a) inflammatory carcinoma, (b) diffuse duct carcinoma, and (c) traumatic mastitis. The initial stages of plasma-cell mastitis resemble inflammatory carcinoma; in the latter state, however, the carcinomatous invasion of the subdermal lymphatics gives rise to an irregular ridge-like thickening of the skin which is not present in plasma-cell mastitis. Diffuse duct carcinoma complicated by inflammation may simulate plasma-cell mastitis, but the disease process is diametrically opposite in the two conditions, one being steadily regressive, the other steadily progressive. Traumatic mastitis is differentiated by the history of trauma and the classical transillumination findings.

There are two pitfalls in the microscopical interpretation, and both apply specially to the examination of frozen sections, in which the fixation is generally inadequate. The intense epithelial hyperplasia often appears to have invaded structures outside normal boundaries. Paraffin sections of the same areas show that the masses of cells are actually confined within normal boundaries of ducts and acini, yet the picture can be so confusing that errors are sometimes made by the most expert. Another source of confusion is that the plasma cells may be so large and oedematous that in frozen sections they resemble anaplastic malignant epithelial cells.

Prognosis and Treatment

This curious unexplained inflammatory process tends to spontaneous regression and resolution, although a remnant often remains for a long time. The possibility that the disease may be precancerous has to be considered, but the clinical evidence is rather against this theory. I have observed one example which was suggestive of a relationship between plasma-cell mastitis and cancer. Adair points out that the time factor has to be considered, and it may well be that further observations will tend to establish a closer relationship between the two states.

The differential diagnosis between the early stages of plasma-cell mastitis and diffuse duct carcinoma with or without inflammatory signs is sometimes difficult. In order to avoid undue delay in establishing the diagnosis, it seems best to perform biopsy early. In former publications I was rather against biopsy during the early acute stage of the disease, but subsequent experience leads to the opinion that, generally speaking, less harm is done by a carefully performed but adequate biopsy than might be done by delaying a diagnosis of cancer. If the inflammatory process is definitely subsiding there would seem to be an advantage in postponing biopsy for a short period.

The safest treatment during the chronic stage, when the lesion is localized, is to remove the diseased area surgically. If most or all of the breast is involved and the inflammatory signs have disappeared simple mastectomy is indicated. During the acute and early subacute stages, the diagnosis having been established microscopically, irradiation should be given, with the reasonable expectation that the lesion will regress and become more localized. Surgical removal of the remnant can then be performed. The possibility that irradiation alone will suffice has to be considered, but until

more cases have been studied over long periods surgical removal, alone or combined with irradiation, constitutes the safest course to pursue.

Summary and Conclusions

Plasma-cell mastitis is a clinical pathological entity. It is a peculiar inflammatory condition of uncertain aetiology. Its practical importance lies in the fact that it simulates cancer so closely that in the past it has almost always been treated by radical mastectomy. Since the onset and the course of the disease are highly characteristic and unlike those of cancer, a distinction is generally not difficult if one keeps the possibility of this condition in mind and if one elicits a careful history in every case of suspected mammary cancer. As regards treatment, the safest course to pursue after establishing the diagnosis by adequate biopsy is surgical excision during the later stages, when the lesion is localized, and irradiation during the acute or subacute stages followed by conservative surgical excision of the remnant.

A case of plasma-cell mastitis with bilateral involvement is reported in which irradiation demonstrated the lesion to be highly radiosensitive. So far as I know, no example of bilateral involvement has hitherto been recorded under this title.

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TWO COMMON NON-MALIGNANT CONDITIONS OF THE BREAST

THE CLINICAL FEATURES OF CYSTIC DISEASE AND THE PAIN SYNDROME

BY

DAVID H. PATEY, M.S., F.R.C.S.

Surgeon, Middlesex Hospital

The clinician tends to divide pathological conditions of the breast into two big groups: a group composed of well-defined pathological entities such as abscess, fibro-adenoma, or carcinoma; and a vague, ill-defined group with varying and indefinite symptoms and signs which he tends to lump loosely together under some such title as chronic mastitis. Owing to confusion which sometimes exists about this latter group I have thought it worth while to describe the two common non-malignant conditions of the breast as I see them clinically. I have also reviewed the literature in broad perspective to show how some of the ideas on this group of disorders have arisen. I would like to support the plea of Cheate for the abolition of the term "chronic mastitis," which has lost almost all precision and value; its sole remaining virtue is that no one can agree on a term to replace it. Deaver and McFarland in 1918 were able to collect no fewer than 23 different terms, and many more have been added since. Rather than attempt to burden the literature with still further terminologies I have thought it

best to rely on a purely factual descriptive term for each of the two main varieties of disorder met with.

There are two common non-malignant conditions of the breast met with clinically. The first is a condition with objective clinical signs—*cystic disease of the breast*; the second is a subjective disorder, the one symptom common to all cases being pain, and therefore it is best labelled the *pain syndrome*.

Cystic Disease of the Breast

Cystic disease of the breast is most commonly met with clinically between the ages of 40 and 50; it may be seen in the late thirties or early fifties, but it is rare for it to develop much earlier or much later. Far and away the commonest clinical picture is that of the *apparently solitary cyst*. A woman without any pain or other premonitory symptoms suddenly happens to feel a lump in her breast. In some cases the patient feels convinced that the lump was not there a short time before, and that it came up suddenly.

On examination the breasts appear normal in all respects on inspection and palpation except for the presence of the lump—hard, smooth, rounded, and with a characteristic dome-shaped top—of a size usually between $\frac{1}{2}$ in. (1.9 cm.) and 2 in. (5 cm.). Elasticity and fluctuation are exceptional. There may be a faint suggestion of lobulation in the form of a slight groove, but not nearly of the degree met with in a fibro-adenoma. There is no skin dimpling, nor are there other infiltrative signs. The diagnosis is established by aspiration, when anything from 2 ml. to 20 ml. of watery fluid, greyish green by reflected light and reddish brown by transmitted light, is obtained. Following aspiration the lump completely disappears and the breast returns to normal, although in the case of large cysts for a day or two a hollow may be felt in the position of the cysts with condensation of the tissues around. The periods are usually regular and normal, there is nothing in the immediate clinical history to indicate the cause of the development of the cyst, and usually there is nothing of note in previous history or the family history. But it has been known since the days of Réclus and Schimmelbusch that the apparently solitary cyst is an expression of a diffuse condition of both breasts, and it is not surprising, therefore, that further cysts sometimes develop, either in the same or in the opposite breast, which lend themselves to aspiration in the same way as the original cyst.

A woman may not come for medical advice until she has in one or both breasts a number of large cysts similar to the usual solitary type—*multiple cysts*. She may come with clinically diagnosable *diffuse cystic disease* of both breasts—a comparatively rare form. The whole of each breast feels shotty and not unlike the normal physiological type of shotty breast, but differing in that the shotty nodules are larger and coarser, varying in size, and in some cases large enough to allow of the insertion of a small needle and the aspiration of fluid, thus confirming the cystic nature. And finally, forming the most difficult diagnostic problem of all, there is the condition of *small aggregated cysts*. This may occur in breasts that are otherwise normal clinically or in breasts affected with clinically diagnosable diffuse cystic disease. A lump an inch (2.5 cm.) or so in diameter is felt which is hard and irregular, just like a carcinoma but without skin dimpling or other infiltrative signs. The lump is formed by the aggregation of a number of small cysts, each of which may be so tiny that nothing may be obtained on aspiration, thus suggesting that it is a solid mass. The establishment of the diagnosis of this type is usually possible only after exploration and naked eye and microscopical examination.

The Pain Syndrome

The second common clinical group of non-malignant disorders of the breast is the subjective disorder which, as stated above, I think best called the pain syndrome, affecting women from the twenties onwards. There are no objective findings. The pain may be an exaggeration of the normal premenstrual feeling of engorgement and sensitiveness of the breasts, or may be present between the periods as well. In other cases it may bear no relation to menstruation. The pain may affect both breasts diffusely, one breast, or a part of one breast. Any form of breast may be affected. In many of these cases there is the phenomenon of the pseudo-lump—i.e., the suggestion of a lump which can be felt with one method of palpation but not with another. Sometimes it is the feeling of this pseudo-lump by the patient that leads to her seeking medical advice. One other and common feature of cases of this type is the fear of cancer, experienced before and sometimes after complaint of pain. This fear may have to be elicited by direct questioning.

Both cystic disease and the pain syndrome are the commonest non-malignant conditions of the breast, the pain syndrome being slightly commoner than cystic disease, and the two together about equal in frequency to malignant disease.

Historical Review

In most reviews of the literature priority is given to Astley Cooper (1829) for the first important description of cystic disease of the breast. Credit for the first coherent account of cystic disease is usually given to Brodie (1846), but my own impression of Brodie's writing is that he did not clearly distinguish between cystic disease and what we now know as Brodie's tumour (cystic or giant fibro-adenoma). A few years later Birkett (1850) and Velpeau (1856) published monographs on diseases of the breast in which both cystic disease and the pain syndrome are clearly recognized and their main clinical features described. James Paget (1870) was interested mainly in the morbid anatomy of the cysts, which he regarded as obstructive in origin and due to periductal fibrosis, comparing cystic breasts to granular kidneys. This almost certainly wrong view of the origin of cystic disease for long persisted in the literature in spite of the work of Réclus and Schimmelbusch, which showed that cysts were secondary to epithelial changes in the ducts of the breast, and has finally disappeared only with the experimental production of cystic disease by hormones. Bryant (1887) also separated the pain syndrome and cystic disease as distinct entities.

By the latter half of the last century surgeon pathologists had recognized and defined the clinical features of both cystic disease of the breast and the pain syndrome. But the position soon became more complicated with the development of the morbid histological era in the study of breast pathology, especially by Réclus and Schimmelbusch. Réclus wrote a number of papers between 1883 and 1893 on what he called cystic disease of the breast. His main contribution was to call attention to its diffuse and usually bilateral character, and to give a clear picture of its morbid anatomy and histology. To begin with, Réclus regarded the condition as precarcinomatous, and treatment by mastectomy or even bilateral mastectomy as obligatory, but as the result of clinical experience he ended by coming to the opposite view. Schimmelbusch (1892) clearly established the histological features of the disease. He showed that the formation of the cysts was determined by the proliferation of the glandular tissue of the mamma, and as a result suggested the term of "cyst adenoma." And he concluded that if there was any risk of carcinoma

developing it was too small to justify such a drastic procedure as bilateral mastectomy, which was the rational one if prophylactic surgery were to be adopted. König (1893) appears to have been the first to emphasize the commonness of the disease.

By drawing attention to the epithelial changes in cystic disease Réclus and Schimmelbusch unwittingly supported the view which already existed, that the disease was precarcinomatous and dangerous; as a result the advocacy and practice of mastectomy increased. Most authors, however, did not carry their logic so far as to advocate bilateral mastectomy. From their time, too, the practice of grouping together cystic disease and the pain syndrome as different phases of the same condition became more general. The classic monograph of Cheatle and Cutler (1931), with its detailed study of the histological changes of cystic disease, was careful to point out once again that the pain syndrome which they called mazoplasia was a separate condition and not precarcinomatous. (Cheatle and Cutler's work was also noteworthy for pointing out authoritatively that nodularity of the breasts is not necessarily pathological; it occurs regularly under physiological conditions such as menstruation and may result from change in the supporting fat of the breast.) Among the latest writers who under the influence of histological appearances regard cystic disease of the breast as precarcinomatous is Willis (1948). But the clinical evidence to the contrary has always been very strong. I previously reviewed this question in 1939, and would refer readers to this review and to Geschickter's (1943) monograph for further references. But to take the most important observations, Bloodgood (1931), who throughout the early part of the century wrote many papers on the subject, reported a follow-up for periods of up to 30 years of more than 100 patients from whom blue-domed cysts had been removed, and found none had developed cancer. Campbell (1934) refers to 233 cases of "chronic mastitis" treated by local excision of areas of breast tissue and followed up for from 2 to 14 years. In one patient only did carcinoma of the breast develop. Geschickter found no cases of carcinoma in 231 cases of the pain syndrome followed up for many years, and only four cases of carcinoma in 378 cases of cystic disease. It is not surprising, therefore, that for many years now clinicians have tended to conservatism in the treatment of both cystic disease and the pain syndrome, and that mastectomy is rarely performed for these conditions, and still more rarely the only logical prophylactic procedure—bilateral mastectomy.

From 1930 onwards many investigators have shown that a cystic disease may be produced in the breasts of animals, chiefly mice and rats, by large doses of oestrogenic substances and that under certain conditions carcinoma of the breast may supervene (see review; Patey, 1939). Geschickter (1943) has more recently summarized his own extensive personal experimental work as well as reviewing the literature. But the application of this experimental work to human cystic disease is not clear in the field of aetiology or of treatment. Thus Bucher and Geschickter (1941) say, "It is not possible to state with assurance the endocrine disturbance in cystic disease,"—i.e., human cystic disease. And Taylor (1942) notes, "In spite of much discussion of chronic mastitis as an endocrine disease, no one has yet succeeded in proving that this breast condition represents a specific response to any recognized type of glandular dysfunction." And it is a matter of common observation that neither in cystic disease nor in the pain syndrome is there any undue frequency of menstrual disturbance. While Spence (1940) thought that testosterone injections and inunctions helped the symptoms of the pain

syndrome, he had improvement in some cases from the inunction of bland ointments; and Atkins (1940) and Taylor (1942) are among those who have found hormonal treatment of this group of disorders of little practical value.

Discussion

Three important questions arise: Are the conditions both manifestations of the same disorder, or are they two separate disorders? What is their cause, or causes? What relation, if any, have they to carcinoma?

As to the first question, there is such a striking clinical difference between the patient with a cyst and the patient with the pain syndrome whose breasts show no clear objective features to distinguish them from any normal woman's that the clinician can only answer that they are separate conditions.

Under the second question, therefore, we have to consider two questions—What is the cause of cystic disease? and, What is the cause of the pain syndrome? The fact that cystic disease predominantly affects women of between 40 and 50 suggested to clinicians long ago that it was related to the hormonal changes occurring at that time, and Deaver and McFarland had suggested that they should be termed "involution cysts." But hormonal disorder is still a hypothesis although supported to some extent by experimental work. The pain syndrome, being a subjective disorder, is most likely to have a subjective cause, and here at once the most striking feature is fear of cancer. In many cases the fear of cancer is clearly the origin of the whole trouble. In other cases, but less frequently, the fixation on the breast is determined by an injury or some previous disease of the breast. But in a small proportion of cases the origin may be psychosexual. Quite accidentally in one of my cases a patient raised the question whether it might be due to a sexual maladjustment with her husband. And since then I have come across a number of similar cases—e.g., the young married woman who wants children while her husband does not; the woman married to a husband much less passionate than herself; and cases with difficulties in the sexual act. I have never regarded it as within the province of the surgeon to make routine inquiries into the sexual life of patients who come with breast troubles. And in those cases of the pain syndrome which I cannot explain on the usual fear-of-cancer basis I tell the patient that some cases of pain in the breast are due to sexual maladjustment or anxieties. Some patients will then wish to discuss further possible factors on these lines; others will not. In any case the bringing of this explanation into the open will often have a beneficial effect. Any deeper exploration of the psychosexual upset is the concern of the psychiatrist rather than the surgeon. At the present time it is not possible to say whether psychosexual factors act on the breast through nervous or through hormonal influences. It is possible that both factors are involved.

Finally, we must attempt to answer the question, What is the relation, if any, of these disorders of the breast to cancer? The pain syndrome, being a functional condition without organic basis, must clearly be quite unrelated to carcinoma. The views of various authorities on cystic disease have already been given. But the strongest support for the now predominantly held clinical view that cystic disease is not a dangerous condition likely to develop into carcinoma is the experience of many surgeons all over the world who for years have treated the condition by some simple procedure such as tapping, with its demonstration that these conservatively treated breasts do not show any special liability to develop carcinoma.

Summary

Chronic mastitis is a term which has lost all precision and value and should be abolished. There are two common non-malignant conditions of the breast met with clinically—cystic disease and the pain syndrome—which are separate and distinct conditions. Cystic disease presents clear objective physical signs from which a clinical diagnosis can be made, the cause is unknown but is possibly a hormonal upset, there is no special liability to carcinoma of the breasts affected, and tapping is a satisfactory treatment. The pain syndrome is a purely subjective disorder, although sometimes superimposed on exaggerated physiological premenstrual engorgement of the breasts, and the breasts affected present no objective abnormality. The cause of the fixation on the breast is usually fear of carcinoma, but in a small proportion of cases is a psychosexual upset. Treatment by explanation and reassurance usually results in cure of the pain.

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AMETHOCAINE HYDROCHLORIDE

SEVERE TOXIC EFFECTS WHEN USED FOR BRONCHOSCOPY

BY

C. A. JACKSON, F.R.C.S.

Chief Assistant, St. Bartholomew's Hospital Chest Unit,
 Hill End Hospital and Clinic, St. Albans

Amethocaine hydrochloride is increasing in popularity in this country as a surface analgesic. The occurrence of two severe toxic reactions arising from its use in a thoracic unit while securing analgesia for bronchoscopy has emphasized again the danger of overdosage when applied to a mucous surface, together with a specific sensitivity shown by certain individuals. These near tragedies have prompted me to review similar cases reported in the literature and to study the properties of this drug. Since amethocaine has been used for surface analgesia twelve deaths at bronchoscopy and gastroscopy have been reported by various authors and a further three deaths during preparation for urethral instrumentation.

Whether it be due to sensitivity or overdosage, the nature of the reaction reveals a striking similarity in the majority of cases and is the typical classic picture of cocaine or procaine intoxication. Within a few moments of local application the patient becomes faint and giddy, and unconsciousness follows. There may be wandering or deviation of the eyes. A trembling and twitching of the extremities occurs

which rapidly develops into generalized clonic convulsions, epileptiform in nature, during which cyanosis, foaming at the mouth, and an accelerated weakened pulse are noted. This seizure may subside with recovery or may return with a greater violence, when the patient may succumb from respiratory or cardiac failure.

Cases in the Literature

There have been a number of case reports in German and American journals since 1935 giving instances of severe constitutional disturbances and even fatalities. Apart from two deaths recorded by Hancock (1939), the only British report is found in a statistical review of causes of sudden death in which two fatalities are recorded as having occurred when this analgesic was being used in bronchoscopy.

In 1939 Fasselt reported two reactions to amethocaine 2% in anaesthetizing the throat before the removal of foreign bodies by bronchoscopy. All symptoms, however, disappeared spontaneously in these cases. Phillips and his associates (1941) reported a similar reaction in a patient who was undergoing a bronchoscopic examination. In this case generalized tonic contractions occurred which were controlled by "dial," 2 ml., given intramuscularly; the strength of the solution was not mentioned. The patient recovered.

Schoen (1939) reported three fatal reactions to local analgesia using amethocaine prior to bronchoscopy. Wagener is reported by him to have quoted a case in which 6 ml. of 2.5% solution was applied to the larynx for the removal of a wart and in which general convulsions occurred, leading to death in six to eight minutes.

In a case quoted by Cazzaniga (Schoen, 1939) a total dose of less than 130 mg. of amethocaine was used, yet the patient, a 27-year-old woman with pulmonary tuberculosis, developed severe convulsions some seconds after the initial administration and death occurred thirty minutes later.

Freeman (1939) reported four serious accidents with amethocaine employed as a mucous membrane analgesic for gastroscopy. Hancock (1939) had two deaths from the drug, also used for gastroscopy. His patients were both in advanced cachexia from malignant disease of the stomach.

Pfeiffer (1937) and Shumacher (1941) reported sensitivity to 0.5 and 1% solutions when administered in the eye. Videbeck (1936) mentioned three cases of amethocaine eczema in doctors who used the drug in their practices.

Thomas and Fenton (1943) provide a series of cases of their own in which amethocaine was shown to possess definite toxic properties. The first patient gave a history of asthma but no history of drug sensitivity. During bronchoscopy, while receiving a second spray of amethocaine 2% five minutes after the first, he had a sudden severe asthmatic attack and died thirty minutes later. A woman giving a history of pulmonary tuberculosis of one year's duration and with no known allergy, after receiving 5 ml. of amethocaine solution by pharyngeal spray became faint and suffered a generalized convulsive seizure with frothing at the mouth, which persisted until respirations ceased. Two other patients, both women, underwent bronchoscopy with amethocaine local analgesia for investigation of bronchiectasis. Feeble respirations, cyanosis, weak pulse, and clonic convulsions developed in both patients. Only after the administration of adrenaline and oxygen did these patients return to consciousness. In both cases skin tests for amethocaine sensitivity proved positive when performed afterwards. A 58-year-old man, after a gastric resection for carcinoma, was being prepared for gastroscopy with a 2% amethocaine gargle, to be followed by a 5-ml. spray, this to be repeated