

Nipple discharge

Key points and new developments

1. The visual assessment of the discharge is still of prime importance because it correlates with clinical significance.
2. Of the three groups, milk (galactorrhoea), coloured opalescent discharge and blood-related (serous, bloodstained and watery) discharge, only the third group carries a risk of serious breast disease.
3. Galactorrhoea is most commonly due to mechanical breast stimulation or drugs, and rarely to prolactinoma.
4. Blood-related discharge is usually due to papillary lesions (duct papilloma or carcinoma) or duct ectasia (DE).
5. Duct papillomas fall into three main categories: 'solitary' papilloma, in major ducts and with little malignant risk; multiple papillomas, in peripheral ducts with risk of recurrence and malignancy; and juvenile papillomatosis, a rare but distinctive condition.
6. Galactography is gaining popularity, in spite of few data on effectiveness – cost and therapeutic – with routine use.
7. Galactography is also combined with adjunctive techniques, such as hook-wire insertion, and ultrasound-guided fine needle aspiration (FNA) or percutaneous dye injection.
8. High-resolution ultrasound, fiberoptic ductography and intravenous enhanced MRI galactography appear to be promising developments.
9. Ductolobular segmental resection is sometimes an alternative to the standard operations of microdochectomy or major duct excision.
10. There is some evidence of increased risk of malignancy with benign papillomas, but not sufficient to warrant routine long-term follow-up.

Introduction

Nipple discharge is important when it occurs spontaneously and as the dominant symptom. Spontaneous presentation is important, because a high incidence will be recorded if milky discharge that occurs only following squeezing or expression of the breast is included in series of patients with nipple discharge. Such a discharge is common in parous women and will often be reported on direct questioning. This is not galactorrhoea and can be safely ignored.

Nipple discharge loses its significance when it is accompanied by a dominant lump. The lump then takes precedence in assessment and management.

A patient may present with discharge because she fears she may be developing malignancy, because the amount may be sufficient to cause social embarrassment, or as an incidental accompaniment of other breast symptoms. In general, the patient will delay no longer before presenting with discharge than with a lump.

Management will be directed at relieving the patient's concern regarding malignancy, and providing treatment

for the minority of women who require treatment for the discharge itself. The ratio of patients falling into the two groups varies considerably in the literature because of different referral patterns and different views as to what constitutes discharge. For example, Gulay et al.¹ found that with an overall referral rate of 5%, the nipple discharge was spontaneous in only half; the other half had expressed the discharge themselves. In some African and Asian countries, nipple discharge accounts for a smaller proportion of referrals.²

Definition

Nipple discharge is defined as spontaneous efflux of fluid from the nipple apart from the physiological function of the puerperium and lactation. Discharge can be elicited by squeezing in about 20% of patients, and application of negative pressure with a pump can increase this to 50%.³ Some patients report that nipple discharge follows mammography.

This chapter considers spontaneous nipple discharge in the absence of a dominant lump. In the latter case, the lump takes precedence in assessment and management. An associated discharge does not increase the likelihood of a mass being malignant at any age.⁴

Several conditions may simulate nipple discharge, especially skin exudate as from eczema of the nipple, and discharge from Montgomery's tubercles, seen particularly in adolescent girls.

Incidence

Nipple discharge is a relatively uncommon presenting complaint in a breast clinic. Devitt⁵ has reviewed the literature of nipple discharge in breast clinics. About 5% of referrals are concerned with this symptom, and of these about 5% will prove to have cancer. Haagensen⁶ reported that 3% of patients referred to him complained of nipple discharge. Our own experience is that 6.4% of referrals were for nipple discharge (Table 13.1). Since many of these cases fall outside the guidelines produced for general practitioner referrals to hospital in the UK⁷ it seems likely that many are unnecessary. The guidelines recommend referral for cases in women over 50 years, for younger women with bloodstained discharge, and for persistent single duct discharge. The BRIDGE study group (1999)⁸ in South Wales found that 5.5% of breast consultations,

Table 13.1 Diagnosis and type of discharge

Referred cases	4012
Nipple discharge	259 (6.4%)
Cancer	14: 57% bloody
Duct papilloma	15: 60% bloody
Duct ectasia	87: 17% bloody

Table 13.2 Relationship of discharge type and pathological diagnosis

Type of discharge	Main cause	Less common cause
Blood-related Bloody	Hyperplastic lesions ^a	Duct ectasia, pregnancy
Serous Watery	Hyperplastic lesions Hyperplastic lesions	Duct ectasia Duct ectasia
Coloured opalescent	Duct ectasia	Cyst
Milk	Physiological	Galactorrhoea of endocrine origin

^aHyperplastic lesions include hyperplasia, papilloma, carcinoma in situ and invasive ductal carcinoma.

in general practice, were for nipple discharge. Seltzer⁹ reported an incidence of 9% in 10 000 self-referred patients.

Leis¹⁰ reported that 7.4% of 8703 breast operations were performed for the indication of nipple discharge. In a study from Guy's Hospital over a 10-year period, 6.6% of referrals were for nipple discharge and of the 6000 operations performed 4.5% related to treatment of nipple discharge.¹¹

Character and significance of discharge

The character of the discharge should be recorded accurately, as a good correlation exists between macroscopic appearance and underlying pathology (Table 13.2). Failure to be specific has led to confusion in much of the literature.

Nipple discharge can be assigned to one of four groups:

- Physiological galactorrhoea
- Secondary galactorrhoea
- Coloured opalescent (or grumous)
- Serosanguineous and watery.

Only the last carries a risk of serious breast disease. The commoner causes of the different types of discharge are given in Table 13.3.

Galactorrhoea

The thin, off-white, modestly opalescent quality of human milk is characteristic. There is a 'grey' area between milk and the thicker creamy discharge of duct ectasia (DE), but it is not commonly difficult to distinguish the two.

Physiological galactorrhoea

Galactorrhoea is defined as milk secretion unrelated to breastfeeding. Many patients complaining of milky discharge are suffering from physiological rather than pathological conditions. Pathology within the breast is so rarely

the cause of the discharge within this group that the cause should be sought elsewhere.

Milk production may continue long after lactation has ceased and a regular menstrual cycle has been re-established. This discharge is usually bilateral and may occasionally be copious. It is of no pathological significance and is usually due to stimulation of the breast by continued maternal attempts at expression. This is sometimes carried out in the belief that it will prevent further milk production, or that milk should not be allowed to lie in the breast. Milk discharge may result from mechanical stimulation of the breasts during sexual activity, especially in young girls. Milky discharge associated with other mechanical forms of stimulation is occasionally encountered, explaining the anecdotal reports of successful breastfeeding in the absence of prior pregnancy, and even reports of successful suckling by men!

Treatment is by reassurance and explanation of the sequence of events, that the condition is self-limiting and that cessation of expression or other mechanical stimulation will allow resolution. Occasionally, physiological milk discharge is seen at the extremes of reproductive life. At the menarche, during the period of rapid breast development, and at the menopause, squeezing of the breasts

Table 13.3 Causes of nipple discharge

	Blood related			Opalescent	Milk
	Bloody	Serous	Watery		
PHYSIOLOGICAL					
Neonatal	–	–	–	–	+
Lactation	–	–	–	–	+
Pregnancy	±	–	–	–	+
Postlactational	–	–	–	–	+
Mechanical stimulation	–	–	–	–	+
Hyperprolactinaemia	–	–	–	–	+
DUCTAL PATHOLOGY					
Duct ectasia	±	±	±	+	–
Cysts	–	–	–	+	–
Papilloma	+	+	±	–	–
Cancer	+	+	±	–	–

+, common or likely cause; ±, rare but well defined; –, unusual or unknown.

may produce small quantities of fluid. Again, explanation and reassurance are all that is required.

The appearance of 'witch's milk' in the neonate has been dealt with in Chapter 3 and is due to the transplacental transport of maternal lactogenic hormones.

Secondary galactorrhoea

The appearance of a milky discharge is occasionally seen apart from the conditions mentioned above. A careful history and examination will usually reveal the cause (Table 13.4).

These causes are mostly related to those situations in which there is an increase in the levels of circulating prolactin. The important causes are prolactinoma and various drugs. Vorherr¹² reviewed the literature and gives a list of 17 causes of galactorrhoea. It is likely that some of these are in reality pituitary microadenomas secreting prolactin, a condition which was unrecognized at the time of the original descriptions. The diagnosis of prolactinoma is suggested by the history of galactorrhoea, amenorrhoea

and relative infertility. If the tumour is large, expansion of the pituitary fossa, and possible erosion of the floor of the sella, may be seen on radiography and help to confirm the diagnosis. More often the lesions are microadenomas and skull radiology is normal. Diagnosis is then dependent on dynamic hormonal studies of prolactin, and on imaging of the pituitary fossa. The galactorrhoea disappears following appropriate treatment with a dopamine agonist such as bromocriptine or cabergoline.¹³ Surgical removal of the adenoma may be indicated in some patients.¹⁴

Drug-induced galactorrhoea is not uncommon and occurs with a number of tranquillizing agents, particularly of the phenothiazine group, oral contraceptives and antihypertensives as well as drugs which have a direct action on the hypothalamic-pituitary axis such as domperidone and metoclopramide.¹⁵ The mechanism of action of some of these changes is obscure. Drugs which have been implicated in the production of galactorrhoea are listed in Table 13.4.

In clinical practice, quite gross galactorrhoea can occur for which no cause can be found on extensive investigation, or on long-term follow-up.

Table 13.4 Causes of galactorrhoea

PHYSIOLOGICAL
Mechanical stimulation
Extremes of reproductive life (puberty, menopause)
Postlactational
Stress
DRUGS
Association with hyperprolactinaemia
Dopamine receptor-blocking agents
Phenothiazines, e.g. chlorpromazine
Haloperidol
Metoclopramide, domperidone
Dopamine-depleting agents
Reserpine
Methyldopa
Others
Oestrogen (including the contraceptive pill)
Opiates
PATHOLOGICAL
Hypothalamic and pituitary stalk lesions
Pituitary tumours
Adenoma
Microadenoma
MISCELLANEOUS
Ectopic prolactin secretion (e.g. bronchogenic carcinoma)
Hypothyroidism
Chronic renal failure

Coloured opalescent discharges

It is generally agreed that all coloured opalescent discharges, after sanguineous discharges and milk have been excluded, may be put into a single group in relation to significance. In particular, they are associated with no increased cancer risk. Such discharges are common in late reproductive life, often intermittent, sometimes persisting and occasionally very profuse. Multiple ducts of one or both breasts are often involved and with discharge of differing appearance from individual ducts. They show a wide range of colours and consistency from a creamy purulent appearance through yellow, brown, green and black. In general, the brown, green and black discharges tend to be of fluid consistency, the creamy discharge is more grumous, sometimes as thick as toothpaste (see Fig. 11.4). The coloured discharges resemble the range of appearances seen in cyst fluid (see Fig. 10.3).

When a pathological entity can be defined, this is most commonly due to duct ectasia (see Ch. 11). At operation for DE, it is noticeable that some ducts are of normal calibre and others dilated, while the material in adjacent dilated ducts of the same breast will be of widely differing appearance; creamy, brown and green material may be seen in the same patient.

Nipple discharge associated with DE is dealt with further in Chapter 11.

In some cases, nipple discharge is clearly due to cysts; occasionally, a ductogram for nipple discharge will show the dye entering a cyst from the duct (Fig. 13.1). Other circumstantial evidence in support of this view comes from patients who relate the appearance of nipple discharge to the disappearance of a previously palpable lump, sometimes during mammography.

Coloured discharges are usually readily distinguished from sanguineous ones, but where a brownish discharge causes difficulty a urine dipstick to test for blood is helpful.

Composition of coloured opalescent discharges

Ogan et al.¹⁶ have studied the biochemical nature of these discharges. They found that nipple discharge fluid usually contained casein, suggesting that such discharges are derived from glandular epithelium secreting milk. Petrakis et al.¹⁷ have measured nipple aspirates for the presence of GCDFP-15, a marker for apocrine metaplasia. GCDFP-15 was found in all but one of 115 women. This suggests that gross cystic disease fluid and nipple duct fluid have a similar composition and therefore a common origin. Petrakis et al.¹⁸ extensively studied nipple aspirates from both asymptomatic women and those with benign breast disease. They found no difference in the constitution with respect to lactose, Na⁺, K⁺ and colour; they did,

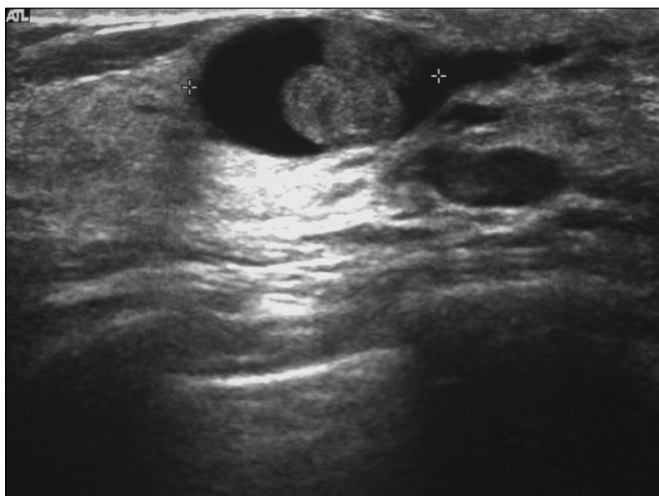


Fig. 13.1 Intraductal papillomata; ultrasound image of two small papillomata within a distended duct close to the nipple; patient presented with discharge.

however, find changes that were age related. Lactose concentrations fell with age while the discharges became darker. In a previous study, Petrakis et al.¹⁹ considered that the colour was likely to be due to pigmented products of apocrine gland secretion, lipofuscin complexes of peroxidated lipoprotein and breakdown products of haemoglobin. Interestingly, they also showed a positive correlation between smoking and dark colour of discharge.

Blood and serosanguineous discharge

Serous discharge is characterized by the yellow colour and sticky quality of serum (Fig. 13.2). Serous, serosanguineous (pink) (Fig. 13.3) and heavily blood-stained discharges (Fig. 13.4) carry the same significance.

Such discharge is due either to a hyperplastic epithelial lesion or to duct ectasia. The epithelial hyperplasia is usually benign, one or more duct papillomas, less commonly malignant. The risk of malignancy increases with age, being much greater after 55 years than before the menopause. In the original series of Selzer et al.⁴ the overall incidence of cancer in patients presenting only with nipple discharge was 12%. The incidence of cancer was 3% in patients under the age of 40, 10% between 40 and 60 and 32% for patients over 60 years.

In patients with duct ectasia, it is assumed that the bleeding arises from areas of ulceration within the stagnant ducts, although we are not aware of any formal study of this question.

In many series, a percentage of cases with sanguineous discharge show no clear-cut pathology, even after operations such as major duct excision. Hence, it is not surprising that conditions of low specificity in pathological terms have been invoked to explain the bloody discharge. Older series often specify cystic disease as the cause. Some seem to refer to macroscopic cysts, others to the micro-papillomatosis element that we now regard as part of aberrations of normal development and involution (ANDI). With these conditions that are part of the spectrum of normality, specificity as to the cause of bleeding is suspect, and the same must be true of a condition as common as DE, the diagnosis we believe to be most common. Hence, the cause of some serosanguineous discharges must remain uncertain, even after surgery. At least the satisfactory long-term follow-up of such cases shows that they are not associated with significant pathology that has been missed at surgery.



Fig. 13.2 Serous discharge, showing the characteristic straw colour.



Fig. 13.3 Serosanguineous discharge, due to a duct papilloma, with characteristic pink colour.



Fig. 13.4 Dark bloody discharge.

Haagensen's experience with serous and bloody discharge showed an identical significance for both types.⁶ Duct papilloma was the cause in 70% and breast cancer in 10%, with both types of discharge. Likewise, 50% of benign papillomas presented with each type of discharge, and cancer cases with nipple discharge were divided evenly between the two. In the Philadelphia series the incidence of cancer was also the same for serous or bloody discharge.⁴ Our experience is similar, although a higher proportion (29%) of our cases of serous or bloody discharge is associated with DE.

Chaudary et al.¹¹ have described the role of routine use of an occult blood test in patients admitted for operation for discharge from a solitary duct. In 292 microdochectomies, 215 were positive for blood. All 16 carcinomas were in this group but, in the benign conditions, the presence of blood did not usefully help to distinguish DE from benign papillomas.

Postsurgery nipple discharge

Lee et al.²⁰ draw attention to spontaneous nipple discharge that appears shortly after breast surgery. It can be due to communication with the operation site, or to a second undiagnosed pathology. Galactography was helpful in demonstrating a communication with the operation site, and the discharge subsequently ceased spontaneously.

Blood-stained nipple discharge of pregnancy

A little-recognized problem that occurs occasionally in pregnancy is bloodstained nipple discharge due to epithelial proliferation as the breasts respond to pregnancy. At term, the proliferation ceases, the cells swell and develop into secretory cells under hormonal control from prolactin, and milk is produced.

This bloodstained discharge is typically bilateral, as have been the cases in our experience, but can be unilateral, when it occurs in the larger of the two breasts.²¹ It usually starts in the second or third trimester of the first or second pregnancy. When bilateral, the condition carries no serious significance and requires simple explanation and reassurance that it is self-limiting. It rarely persists for more than 2 months postpartum.²² Further investigation and treatment should be avoided because cytology may be misleading in this situation. It often shows epithelial cell clusters similar to those of intraductal papilloma and the cells may appear to be cytologically active.²³ As it is

self-limiting and disappears with breastfeeding, firm reassurance is all that is required.

It has been suggested recently that bloodstained discharge from a single breast during pregnancy should also be managed expectantly. Lafreniere²¹ has reviewed the literature and found no example where this symptom has led to a subsequent diagnosis of cancer. This is reassuring, although clinical judgement should be exercised in a unilateral case. Breast examination and monitoring with ultrasound might be wise.

Watery discharge

This is a rare but very distinctive type of discharge (Fig. 13.5) which carries the same significance as serous or bloodstained discharge.

Why a blood-related discharge should be watery rather than serous is not obvious. It is crystal clear, copious and associated in our experience in four cases with multiple papillomas of the large ducts: with macroscopic papillomas in one case and with florid microscopic papillomatosis in the others. As yet, none has developed cancer (after 5 years of follow-up). Haagensen believes the large papilloma condition to be premalignant, although he could only record one such case, which was associated with papillary intraduct cancer. We have also had a case where the only pathology on duct excision was a gross degree of DE. Lewison and Chambers²⁴ present evidence that this type of discharge is associated with breast cancer and Leis¹⁰ found cancer in a third of 15 cases with watery discharge.



Fig. 13.5 Clear watery discharge, distinct from serous and sanguineous.

Pathology underlying nipple discharge

Duct papilloma

Benign duct papillomas occur in three main forms: solitary (discrete) duct papilloma, multiple duct papillomas and juvenile papilloma. These are three reasonably discrete clinicopathological complexes, but because of overlapping features, these terms are not ideal in terms of descriptiveness or specificity. For example, 'solitary' duct papilloma is often multiple. However, these are the terms proposed by Haagensen, who was primarily responsible for defining the three conditions. As these are now in general use and we cannot suggest better terms, we retain them. Being familiar with, and understanding, the three clinicopathological pictures and their implications is the priority, so that a patient can be put into the appropriate group.

It is also important to differentiate these macroscopic lesions from the microscopic papillary hyperplasia often referred to in the past as papillomatosis in the American literature, and as hyperplasia or epitheliosis (without atypia) in the British literature. This latter condition, part of ANDI, is not related to the duct papillomas described here.

In summary, discrete 'solitary' papillomas are the most common of the three; they occur in a large subareolar duct, frequently cause blood-related nipple discharge, and have little malignant potential. Multiple papillomas are rare, more peripheral, less likely to cause nipple discharge and have greater malignant potential. Juvenile papillomatosis is an exceedingly rare condition with yet another clinical picture.

Solitary (discrete) duct papilloma

The commonest hyperplastic lesion causing a serous or sanguineous discharge is discrete duct papilloma: single or multiple. The defining feature is its occurrence in a large duct. In about half the cases, the discharge is bloody; in the other half it is serous. A subareolar lump is palpable in less than half of the cases. The history is sometimes a long one; the discharge may have been present for several years.

The typical ductal papilloma is just 2–3 mm in diameter (Fig. 13.6), but as it grows it elongates and extends along the duct system so that it may be 1 cm or more in length.

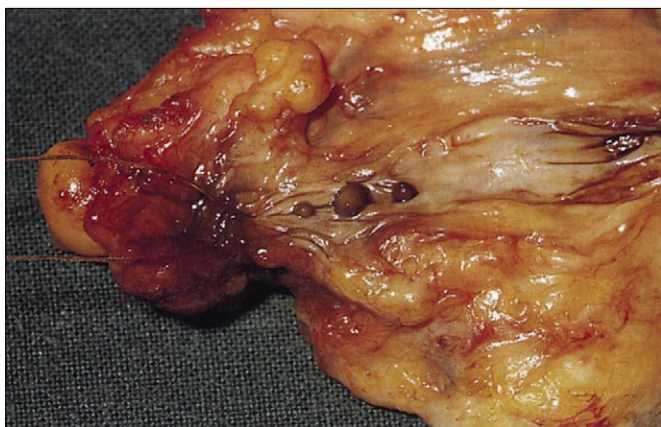


Fig. 13.6 Microdochectomy specimen opened to show three small duct papillomas.

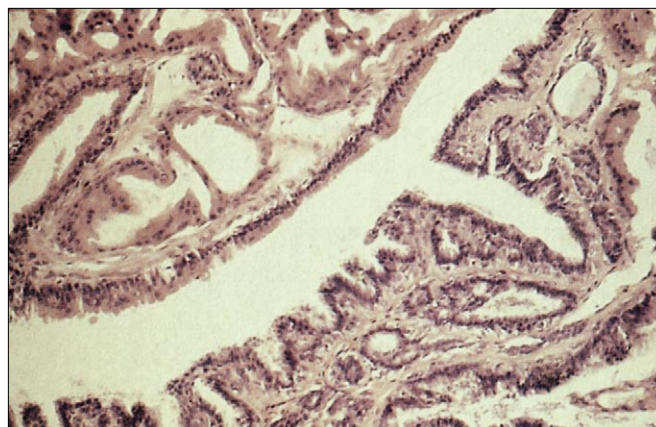


Fig. 13.8 Histology of benign large duct papilloma showing the typical core vascular stroma with covering epithelium.

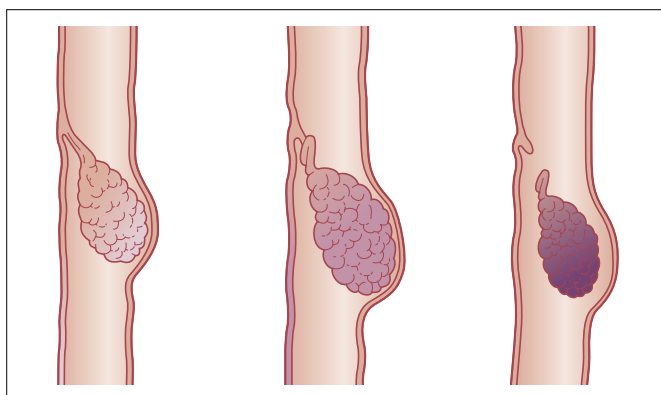


Fig. 13.7 Schematic representation of torsion and infarction of a duct papilloma.

Larger papillomas tend to cause, and lie within, a local pocketing of the duct, a diverticulum which alters the normal line of the duct. Fine probes passed into the duct tend to get side-tracked into these diverticula. The papilloma has a narrow, fragile stalk and delicate fronds. The narrow stalk predisposes to torsion, which may result in infarction and this is not uncommonly seen on histology. It is presumably the reason why bloody discharge frequently remits spontaneously, particularly in young women. The sequence of events is summarized in [Figure 13.7](#).

The delicate fronds account for the marked tendency to haemorrhage. As the papilloma elongates and grows along the duct, torsion becomes less likely but partial ischaemia may lead to fibrosis and adhesion to the duct wall, making differentiation from papillary carcinoma

more difficult. Some authorities believe this to be the origin of ductal adenoma. Typical small lesions have many fronds with a fibrovascular core and a covering of regular epithelium, although mitoses may be quite frequent ([Fig. 13.8](#)).

Although a well-known lesion, solitary papilloma is relatively uncommon. There were only 15 'solitary' duct papilloma cases in the 259 nipple discharge patients in our Cardiff study and the figure of 29% of operations for nipple discharge is similar to the 37% of operations for nipple discharge described by Leis.¹⁰ Most papillomas appear in the fourth to sixth decades with a peak age incidence in the fifth decade. However, it has a wide range of age incidence and we have seen it at the age of 16 and in an octogenarian. Sandison,²⁵ in his postmortem study of 800 women, found an incidence of duct papilloma of 1.6%. This suggests that many papillomas go undetected through life.

The usual location of a duct papilloma is in the subareolar major ducts, within 5 cm of the nipple. Macroscopic papillomas are usually solitary, but it is not uncommon to find two or three distinct papillomas in the one segment of duct (see [Fig. 13.6](#)). In fact this is commoner than most reports suggest, and depends on the assiduousness with which the duct is dissected (and the state of the specimen presented to the pathologist!). This is also the reason why the term 'solitary' papilloma is not entirely appropriate; perhaps 'discrete' is a better term since each is a small discrete lesion as seen in [Figure 13.6](#).

In older patients there may be 10 or more such lesions distributed throughout the larger ducts of a single segment, with the whole segmental system distended to

its periphery. But the papillomas remain small, discrete and with benign histology, and so represent the extreme of the spectrum of 'solitary' papilloma. They are still better included in the 'solitary' group than the 'multiple papilloma' group, which has a different clinicopathological picture, as discussed below.

Duct papillomas are sometimes bilateral. Seven of the 173 cases reported in Haagensen's series⁶ were bilateral, and bilateral involvement was simultaneous in one case. In the remainder, the average time to presentation in the opposite breast was 8 years.

Solitary intraduct papilloma is not usually considered to be premalignant. Many recent studies have shown no increased incidence of cancer, but it must be admitted that there is a paucity of sound long-term follow-up data. The American College of Pathologists (ACP) consensus statement²⁶ puts papilloma with a fibrovascular core in the group with a slightly increased risk of cancer.

Occasionally, a papilloma develops in the terminal subareolar duct, when it may distend the nipple or prolapse through the duct orifice on to the nipple. When this occurs, usually in an elderly patient, it requires separation from a distinct entity, erosive papillomatosis (see Ch. 12). The characteristic feature of a prolapsed ductal papilloma is that the surface of the nipple is unaffected. With erosive papillomatosis, the nipple itself is eroded. Haagensen⁶ gives clear guidelines for distinguishing the two.

Multiple duct papillomas

The term 'multiple duct papilloma' is better reserved for the uncommon condition of papillomas occurring in small peripheral ducts. They occur in a ratio of about one case to eight cases of solitary, large duct papilloma. They are more commonly palpable, more peripheral in the breast, more likely to be bilateral and less likely to give rise to nipple discharge than the 'solitary' or discrete type. The condition is of such rarity that few have a significant experience of it, and it is difficult to be certain that the small series reported are homogeneous with regard to the type of cases included.

A distinctive group described in detail by Haagensen differed from common experience in that almost all were large enough to be palpable and clustered together with obvious multiplicity. Haagensen⁶ described 53 examples of this condition and found the mean age to be slightly younger than those with solitary papilloma though with a similar age range of 20 to 70+. A tumour was usually

palpable with a diameter >2 cm, only a quarter were central compared with 90% of 'solitary' lesions, while local recurrence and subsequent carcinoma were respectively 15 and 3 times as common. For this reason, Haagensen considered this lesion to be premalignant, and 15 of his 39 patients developed carcinoma. In general, both benign local recurrence and subsequent malignancy occurred in the same segment of the breast as the original lesion, but this was not always the case. Nevertheless, Haagensen advises a conservative approach, reserving mastectomy (somewhat reluctantly) for multiple recurrences.

In more recent reports, cases have been diagnosed earlier, when tumours are smaller and less likely to be palpable than cases reported by Haagensen, but the implications are similar. Thus, a subclinical variant where tumours are less likely to be palpable may be a halfway house between intraduct cancer and Haagensen's palpable benign tumours. The smaller lesions have common features with the larger ones: multiplicity, peripheral location (often in continuity with the terminal ductal lobular unit, TDLU), and a distinct association with cancer. Because these lesions are uncommon, and reported series are retrospective or of few cases, it is difficult to put together a coherent picture. However, there is a general uniformity regarding a high recurrence rate after local excision, the presence of atypical hyperplasia in association with the lesions,²⁷⁻²⁹ and a considerable subsequent incidence of cancer. Haagensen's series probably included cases of juvenile papillomatosis, which was a less well-defined entity before the publication by Rosen et al.³⁰

In our small experience, this syndrome was associated with a watery discharge, and the tumours involved multiple breast segments. It seems likely that this is often a multisegmental system, in contrast to the unisegmental single duct system involved by 'solitary' papillomas, and this is at least part of the reason for the high local recurrence rate. For this reason it has seemed appropriate to us to advise local mastectomy, with immediate reconstruction where desired, but a more segmental resection seems reasonable where the pathology appears to be well localized.

Juvenile papillomatosis (Swiss cheese disease)

Although most patients with this condition present with a lump rather than nipple discharge it is convenient to consider it here because of its relationship to multiple papillomatosis and doubt about the distinction of these

conditions. Nipple discharge has been described in 15% of cases of juvenile papillomatosis. The clinical diagnosis is often fibroadenoma, because of the age of the patient, and the first suggestion of the diagnosis may come when fine needle aspiration (FNA) produces watery fluid.

Haagensen first described eight patients with multiple intraductal papillomas which were unusual in that they were palpable, occurred in young women (age 14–24) and in which the epithelium was entirely apocrine in nature. He treated all cases by local excision without recurrence.⁶

Rosen and colleagues reported a collected series of 32 cases, and applied the term ‘Swiss cheese disease’ because of the multicystic nature of the masses.³⁰ They started a registry for these cases, and in 1985 gave a further report.³¹ The patients were a little older than Haagensen’s group (mean age 23 years) and typically presented with multiple small masses (1–3 cm) in the upper outer quadrant, sometimes bilateral, and because of the age group, were usually diagnosed as having fibroadenomas. The first suggestion that this might not be so was the finding of watery fluid on FNA. There was a family history of breast cancer in 25% of cases.

Macroscopically, the tumours are firm, cystic swellings with a circumscribed margin, but not enough to shell out at operation. Histology showed benign proliferative epithelium with half the cases showing a degree of histological atypia which would be regarded as precancerous in an older patient. The term papillomatosis is used in the American sense of ‘epitheliosis’; it does not show a papillomatous structure with a central stromal core. A third paper reported follow-up of 41 patients after a mean period of 14 years.³² In this group 58% had a family history (usually mother or maternal aunt) and six of 41 were bilateral. Ten per cent had developed breast cancer, and all of these had bilateral and recurrent papillomas and a family history of breast cancer. So those without these features seem to be at low risk. Complete excision with a small margin is recommended management at present, although recurrence does not seem to show a close relationship to clearance margins. Annual surveillance and breast self-examination are recommended for most cases, with more intensive follow-up for the high-risk cases (bilateral/recurrent/family history).

Papillary carcinoma

Papillary carcinoma is the usual type of malignancy associated with nipple discharge. However, most papillary

carcinomas do not present in this way. Only 26% of Haagensen’s cases presented with a nipple discharge; in 80% it was sanguineous or serosanguineous, and in the remaining 20% the discharge was serous. This diagnosis becomes much more likely over the age of 50 than in younger patients, and forms a continuum with the second type of multiple papilloma described above. This condition is outside the scope of this text but an excellent description can be found in Haagensen’s textbook.⁶

Duct ectasia

Duct ectasia may give rise to blood-related discharges as well as the typical cream/brown/green/black colours. It is uncommon for more than a few of the ducts to be affected. The ducts are usually about 2–5 mm in diameter, often very thin walled but sometimes become thick walled. The discharge varies in consistency from thin to thick to grumous (toothpaste-like), which has to be squeezed out, and the colour is usually creamy coloured but is often brown or greenish. Analysis of the discharge shows fatty crystals and large foamy macrophages and much amorphous cell debris. Pigmented cells termed ‘ochrocytes’ by Davies³³ are also presumed to be macrophages which have ingested the ceroids produced by degeneration of the fatty material in the ducts which gives this type of discharge its wide variety of colour.

It is not always realized that duct ectasia is also a common cause of blood-related discharge, both serous and bloodstained. It is presumed that this arises from small ulcerated areas of duct mucosa. We have also had a case with profuse watery discharge which required major duct excision, and no pathology was found in the specimen except markedly dilated ducts.

The pathology is dealt with in detail in Chapter 11.

Cysts and ‘fibrocystic disease’

It is uncertain how commonly cysts are the cause of nipple discharge. They are undoubtedly responsible in some cases, because injection for nipple discharge may show the duct communicating with the cyst (see Fig. 10.9). Sometimes aspiration of the cyst will be followed immediately by discharge of similar material through the nipple; presumably, release of intracystic tension allows the draining duct to open. Occasionally, the nipple discharge is elicited during mammography. The frequency of multiple duct involvement with coloured opalescent discharge suggests that DE is a more common cause than

cyst, as does the frequency of ectatic ducts at operation where this type of discharge has been seen.

The situation is confused by the fact that cysts have often been regarded in the past as a variant of DE, with both being merely a part of the spectrum of 'fibrocystic disease', especially in the American literature. It is now well demonstrated that cysts arise from lobules, and have a different pathogenesis from DE.

Many series also describe 'fibrocystic disease' as the cause of up to 25% of blood-related discharge. There is no obvious explanation as to the underlying pathogenesis, and since this is no more than part of the spectrum of normality, the possibility that a conservative microdochectomy may have missed the true cause should be considered. With full preoperative evaluation of the patient, including fiberoptic ductoscopy in selected cases, negative histological findings at duct excision become less frequent.³⁴

Nipple discharge in children and adolescents

Duct papilloma is occasionally seen in the later teenage years, but 'nipple' discharge in the earlier years is more likely to come from the surface of the nipple or from the areola. The commonest cause is probably related to Montgomery's tubercles.^{35,36} The discharge may be clear to brown or bloody, with an associated lump. The discharge usually resolves spontaneously over a few weeks, but the lump may take several months to resolve. The cause is not obvious, but may be related to trauma to the duct orifice, since irritating clothing is another cause of nipple discharge in this age group.³⁷ We have also seen bloody discharge from Montgomery's tubercle in an adolescent with no underlying pathology. Again, the probable cause was trauma. Rogerson et al.³⁸ have reported on 16 cases of adolescent areolar discharge but found that in some surgical excision was necessary.

In children under the age of 5, duct ectasia is well recognized, and probably the most common cause of bloody discharge in this age group.³⁹ It is associated with a mass, the histology of which shows cystically dilated ducts with thickened walls and containing acellular material with cholesterol clefts, and blood. The duct lining shows focal ulceration and granulation tissue. Most settle spontaneously, although this may take months. It is particularly important to avoid surgery in young girls; otherwise breast development may be compromised.

Assessment

History

The history will cover duration, frequency, associated symptoms (pain, lump and nipple inversion) and precipitating causes. Careful questioning will usually reveal the nature of the discharge, its spontaneity and whether single or multiple duct openings are involved. Note should be made of menstrual irregularities and medication, particularly oral contraception in young women and hormone replacement therapy in older women. In women with a milky discharge, particular attention needs to be paid to previous lactation, breastfeeding and history of mechanical stimulation of the breast.

Physical examination

A useful sequence is as follows:

- Inspection should reveal whether discharge is from a solitary duct (and, if so, which duct) or from multiple ducts, and the colour and nature of the fluid. It is usually most convenient for the patient to express a little fluid herself while the physician watches. Where discharge is scant, a magnifying glass may be useful. Where no discharge is produced, inspection of the brassiere may reveal sufficient staining to determine whether or not it is sanguineous.
- Palpate slowly and systematically around the areola to determine where pressure will produce discharge and which duct is involved. If this is successful, a smear may be taken for cytology. When the segment has been localized, feel carefully for a palpable mass or dilated duct, especially under the areola. By pinching the areola between finger and thumb an assessment of the bulk of the ductal tissue can be made and the two sides compared.
- Careful standard examination of both breasts and axillae.

Investigations

Mammography

Mammography is advisable in all patients over 35 years with nipple discharge, and particularly so where the discharge is serous, bloody or watery. The most important finding is microcalcification along the line of ducts as it

may draw attention to an otherwise unsuspected intraduct carcinoma. Prominent ducts may be noted together with the coarse, large calcifications which are typical of duct ectasia (see Fig. 11.19).

Galactography

Small papillomas may be demonstrated by cannulation of the duct and injection with contrast material (or by a percutaneous, ultrasound-guided technique if the duct cannot be cannulated⁴⁰) but false positives and false negatives are not uncommon, in spite of some series reporting a strong correlation between radiological and pathological findings.

Debris or blood clot may masquerade as papillomas, while others may be missed in dilated ducts. Baker et al.⁴¹ found that 20% of lesions seen on galactography could not be found in the pathology specimen. Duct injection is distinctly uncomfortable for the patient and, for this combination of reasons, we do not use the procedure as a routine investigation. It rarely alters management, but it does have a role in unusual or difficult cases. Ultrasound-guided FNA can be used to obtain cytology of a lesion demonstrated on galactography, and Sardanelli et al. found this twice as accurate as nipple discharge cytology.⁴²

An extension of the technique is to insert a Kopan's spring-hookwire into the duct at galactography, to facilitate locating a lesion at surgery.⁴³ These authors found the technique satisfactory in 29 of 34 patients; in the other five the wire was dislodged.

Another option is to inject methylene blue into the duct at the time of galactography, to aid the identification of the affected duct system.⁴⁴ This requires galactography to be scheduled on the day of surgery to give maximum effectiveness. A bloody discharge will outline the duct without methylene blue, which can also cause problems if accidental damage to the duct leads to extravasation of the dye into the wound. For this reason, we advocate that no attempt should be made to elicit the discharge in the 24 hours prior to surgery.

In a comparative study of three-dimensional magnetic resonance imaging, ultrasound and galactography in 55 patients Nakahara et al.⁴⁵ found three patients with malignant lesions that were not identified by galactography. The optimum role for galactography remains uncertain.

Ultrasound

In our experience ultrasound has a limited role in assessment of nipple discharge. It may be used to amplify information about palpable or radiological abnormalities defined during initial assessment. Ultrasound can demonstrate dilated subareolar ducts. In the study of Nakahara et al.⁴⁵ ultrasound correlated less well with eventual pathological diagnosis than three-dimensional magnetic resonance imaging.

Fibreoptic ductography

A silica fibrescope of 0.48 mm diameter enables the breast ducts to be directly visualized.^{46,47} Small intraduct carcinomas, intraduct papillomas and other benign lesions can be seen. Pereira and Mokbel⁴⁸ have reviewed the history and likely future developments of this technique, which can be performed as an office procedure under local anaesthetic. While it is an attractive concept it is not yet clear that it offers significant advantage over other diagnostic techniques such as helical computed tomography.⁴⁹ We have no experience of this technique but it would appear to offer an ability to refine the preoperative diagnosis in some cases of bloodstained nipple discharge.⁵⁰

Exfoliative cytology

Cytological examination of nipple discharge has been used for a long time: the first report of diagnosing a carcinoma by this technique was in 1914.⁵¹ This investigation will sometimes indicate intraduct carcinoma as the cause of the discharge. However, there are too many false negatives for it to be regarded as a completely reliable investigation. For example, Kjellogren⁵² found a 16% false-negative and a 4% false-positive rate. Aspiration cytology of any associated mass is obviously appropriate (see Ch. 5) and is considered more reliable.⁵³

Groves et al.⁵⁴ have carried out an audit of nipple discharge cytology and found that although the test has a low sensitivity for carcinoma (46.5%) it does have a high specificity (99.5%). They conclude that this approach is of limited value but in view of the ease with which it may be performed it should not be discarded completely. Dunn et al.⁵⁵ reviewed a 12-year experience in Bristol and found similar sensitivity (55%) and specificity (100%) rates. Two cancers in this series were diagnosed by

cytology alone. This investigation is particularly appropriate for patients with blood-related discharge.

An expanded approach to exfoliative cytology is directed at samples obtained by suction rather than those of spontaneous discharge. Wrench et al. have studied the factors affecting ability to obtain cytological specimens by suction.⁵⁶ Specimens are more likely to be obtained during ages 35–50 years, from women with an early menarche, non-Asian patients (versus Asian) and those with a history of lactation (parity alone has no effect). King et al.³ have shown that it is possible to identify atypical cells as well as those which are unequivocally malignant. However, satisfactory specimens were obtained in less than half of the patients they studied so the value of this technique in routine practice is limited. Because of the very active epithelium in pregnancy, false positives are particularly likely at that time. In a study of 1948 nipple aspirates Gupta et al.⁵⁷ found that 624 had benign cells, 492 were inadequate, 96 were inflammatory, 229 showed papilloma, 22 were suspicious and 67 malignant. The authors concluded that the technique was reasonably specific for malignant disease but it is worth noting that there were two false positives in their 67 malignant cytology (a woman with a fibroadenoma and a man with florid gynaecomastia). It would seem prudent to obtain confirmatory evidence of the diagnosis before proceeding to definitive treatment. Another route to increased cellular material for examination is ductal lavage,⁵⁸ while this technique has been used in association with fiberoptic ductoscopy it remains to be seen if it is helpful in routine practice.⁵⁹ One problem with this approach is that atypical cells identified on one examination may not be elicited on subsequent tests. For example, when Johnson-Maddux et al.⁶⁰ repeated the ductal lavage in 23 patients with atypia on cytology, 13 (52%) had normal cytology on repeat lavage. They conclude that atypia may be artefactual or physiological in many instances.

Cytology may be helpful in confirming duct ectasia, especially when it is associated with periductal mastitis. Large foamy macrophages with few, if any, epithelial cells are typically seen.

In conclusion, we regard cytology of the discharge as useful in those over 35 years old, but as with other tests for malignancy, negative results should be ignored. Sometimes a positive cytology is the sole positive investigation in the assessment of a patient with serosanguineous discharge.

Occult blood testing

In most cases it is easy to determine from the fluid whether it is bloodstained or not. Where there is doubt, use of a Clinistix paper applied to the discharge will give a rapid answer.

Other biochemical tests

Tests for various enzymes and biological markers in the discharge have been described, but cannot yet be regarded as sufficiently discriminatory to enter routine clinical use. An example is that of Inaji et al.,⁶¹ who used the combination of Erb-2 and CEA levels to detect cancer, though with some false-positive results with benign proliferative lesions. Sauter et al.⁶² have developed a predictive model based on clinical findings and the results of a proteomic analysis of nipple aspirate fluid. Such an approach might be of value in those patients in whom a definitive diagnosis of the cause of nipple discharge cannot be obtained by conventional investigations.

Management

The importance of accurate assessment of the nature of the discharge cannot be overestimated, since most patients will have benign disease and can be reassured, some with and some without, investigation. Coloured, opalescent discharges are very common, and can be treated expectantly, as can any discharge which cannot be reproduced in a young woman. Similarly, most galactorrhoea can be ignored if a specific endocrine cause is excluded. Most such discharges will stop spontaneously, and firm reassurance that cancer has been excluded will be satisfactory for most patients. A minority will dislike the discharge so much that they wish to have it stopped even though it carries no serious import. The only reliable method of achieving this is complete division of the duct system, and this procedure is described in Chapter 18. We have no experience of blocking the offending ducts with fibrin as described by Hockel and Klose⁶³ nor can we find any further reports of this technique.

The management of the blood-related group of discharges is more contentious. If cancer can be confidently excluded then an expectant management policy can be followed. The gamut of investigations outlined above now means that diagnostic surgery is rarely required.

Treatment can thus be aimed at securing symptomatic relief.

This is a far cry from recent conventional practice and it is useful to consider the approach to management of nipple discharge from an historical perspective as the philosophy of management of serous or serosanguineous discharge has changed radically. Opinion regarding the likelihood of it being due to cancer was sharply divided early in the twentieth century. Judd,⁶⁴ in 1917, reported a 57% incidence of cancer in 100 cases at the Mayo Clinic. At about the same time, Bloodgood⁶⁵ regarded it as an innocuous symptom due to duct papilloma and not duct carcinoma. Two papers in the 1930s played an important role in influencing the vogue for mastectomy which dominated the mid-decades of the twentieth century. In 1930, Adair reported 108 cases from the Memorial Hospital,⁶⁶ with 47% malignant. In 1931, Cheatele and Cutler⁶⁷ argued strongly from pathological evidence that benign papillomas could progress to papillary carcinoma. This led to simple mastectomy being the standard treatment for blood-related discharge in many clinics.

A more conservative approach is now accepted, resulting particularly from the studies of Haagensen in the USA and Atkins and Wolff⁶⁸ in the UK, who all recognized that those patients whose discharge was due to duct papilloma were cured by removing the papilloma. Both groups recommended conservative operations; Atkins developed the operation of microdochectomy and Haagensen⁶ used a procedure intermediate between the microdochectomy of Atkins and the major duct excision operation of Urban.⁶⁹

More recent series have given a better indication of the likely pathology of these blood-related discharges. Leis's study of 560 patients undergoing breast surgery for discharge showed that only 20% of those with blood-related discharge had cancer or a premalignant condition.¹⁰ Funderbunk and Syphax⁷⁰ give a clear breakdown of the causes of 167 cases of nipple discharge. Of 46 which were opalescent or green, none had cancer or hyperplasia; but of 121 patients with a clear, serous or bloody discharge, 11 had cancer, 11 had 'papillomatosis' (hyperplasia) and 59 had a duct papilloma. Richards et al.⁷¹ have reported a series of 83 patients observed over a 3-year period. All patients with a pathological discharge (defined as blood-stained, serosanguineous, serous or clear) with a normal triple assessment were offered ductal surgery. Two in situ cancers were identified, neither had red blood cells in the discharge and both were over 60. The series shows a

marked relationship between the incidence of cancer and increase in age, as discussed below.

More recently, nonsanguineous discharges have also become better recognized, and management of nipple discharge is now related to a number of factors, particularly the type of discharge, the age of the patient, and whether a blood-related discharge can be localized to a single duct.

General principles of management

Nature of the discharge

If the discharge is milk, look for a cause outside the breast, such as an endocrine cause or continuing mechanical stimulation.

Coloured, opalescent discharges have no serious significance. They should only be treated if causing social embarrassment. In doubtful cases, blood should be excluded by a chemical test.

Blood-related discharges cause much more concern to the patient and are associated with cancer risk. The risk is minimal in young patients but more significant with increasing age. The age of the patient is only important in decision-making

This is important only in blood-related discharges because of the cancer risk. No active treatment is necessary in young patients if the discharge ceases spontaneously. Wilson et al.⁷² followed 74 young women and adolescents and found that none of them developed cancer before the age of 30. The threshold for advising surgical biopsy is clearly lower in older women but even then most women can be assessed preoperatively and be treated conservatively if they so wish. The adoption of a conservative approach to blood-related discharge is dependent on the availability of high-quality imaging and cytological assessment.

Localization

If the discharge can be localized to a single duct, microdochectomy gives satisfactory results in younger patients with minimal interference to the breast. In older patients where breastfeeding is not required, major duct excision may be preferable irrespective of whether the discharge is localized to one duct, both to avoid the inconvenience of further discharge from a different duct and to provide more comprehensive histology.

Specific details of management

The management of nipple discharge is summarized in Table 13.5 and Figure 13.9.

Blood-related discharge: serous, serosanguineous, sanguineous, watery

Under the age of 30, risk of malignancy is low, so the patient may be safely observed after full assessment as above. If discharge persists, and a solitary duct can be identified, the procedure of choice is microdochectomy (see Ch. 18). While standard descriptions of this operation suggest removing approximately 2 cm of duct, the duct excision should be extended into the breast if the duct remains distended at this level. If the discharge ceases and does not recur within a year, no further follow-up is indicated.

When surgery is indicated for patients over 45 our preferred operation is a formal excision of the major duct system (2.5 cm or as far as dilated ducts contain blood/serum) on the affected side (see Ch. 18), with urgent paraffin section. It is important to remember to mark the terminal part of the ducts immediately behind the nipple so that the pathologist can orientate the specimen. The advantages of this approach are that it is not essential to isolate a solitary offending duct; it deals with multiple papillomas if these are present and gives maximum histological information, and it deals with duct ectasia if this proves to be the cause. With well-performed surgery (and in the absence of chronic infection) there is no significant difference in the cosmesis following single or multiple duct excision.

Patients between 30 and 45 are suitable for either approach. In general, they may be treated as for the under-30 age group, but may be moved towards major duct excision by additional factors, e.g. strong family history of breast cancer, a particularly worried patient, or coexisting nipple inversion which the patient wants corrected.

Is it acceptable to avoid surgery in older patients with normal imaging and no mass, as has been advocated by some. The group from Nottingham⁷³ have advocated this approach on the basis that they only found two cases in their retrospective analysis of 97 cases that had not been already suspected on mammography. Other authors demur. For example, Leis¹⁰ found a false-negative rate of 9.5% for mammography and 17.8% for cytology in 84 patients with cancers. Hence, we believe the emphasis should remain on surgical exploration for those judged to be at risk of cancer on the above criteria. Bauer et al.⁷⁴ reviewed the pathological findings in 277 women following surgery for spontaneous blood-related discharge; 15.5% were found to have ductal carcinoma in situ (DCIS). The discharge was bloody in 29, clear in 8 and brown in 6. Lau et al.⁷⁵ reported the results of 118 duct excisions performed between 1995 and 2002 for pathological discharge. Eleven (9.3%) cancers were found although this rose to 12.7% for postmenopausal women. Solitary duct papillomas were found in 25 patients and diffuse papillomatosis in 43. In only 7 cases were they unable to make a formal diagnosis. They too conclude that surgical exploration is advisable even in those without evidence of serious disease on clinical and imaging assessment.

We still recommend surgery in all blood-related cases defined by our criteria set out above. The operation is a minor one and the incidence of previously undiagnosed DCIS too high to be ignored. An alternative approach, at any age, is to perform an ultrasound-guided mammotome excision. This provides an adequate treatment for benign papillomas and allows rational decision-making for those with more aggressive lesions.⁷⁶ One series reported the experience of 77 patients with satisfactory results in 95%. Four patients either required a second mammotome excision or a microdochotomy. It has the added advantage that it can be performed as an office procedure.⁷⁶

Coloured opalescent discharge

This only requires treatment if the amount of discharge is personally embarrassing, with the need to wear pads constantly. The only effective procedure is a total duct excision, and in well-selected cases is welcomed by the patient.

Table 13.5 Management of milky and opalescent discharge

MILK DISCHARGE (GALACTORRHOEA)
Eliminate mechanical stimulation
Stop or change medication
Measure serum prolactin
Reassure
COLOURED OPALESCENT DISCHARGE
Exclude blood
Mammogram to exclude other pathology (over age 35 only)
Reassure
Major duct excision if socially embarrassing

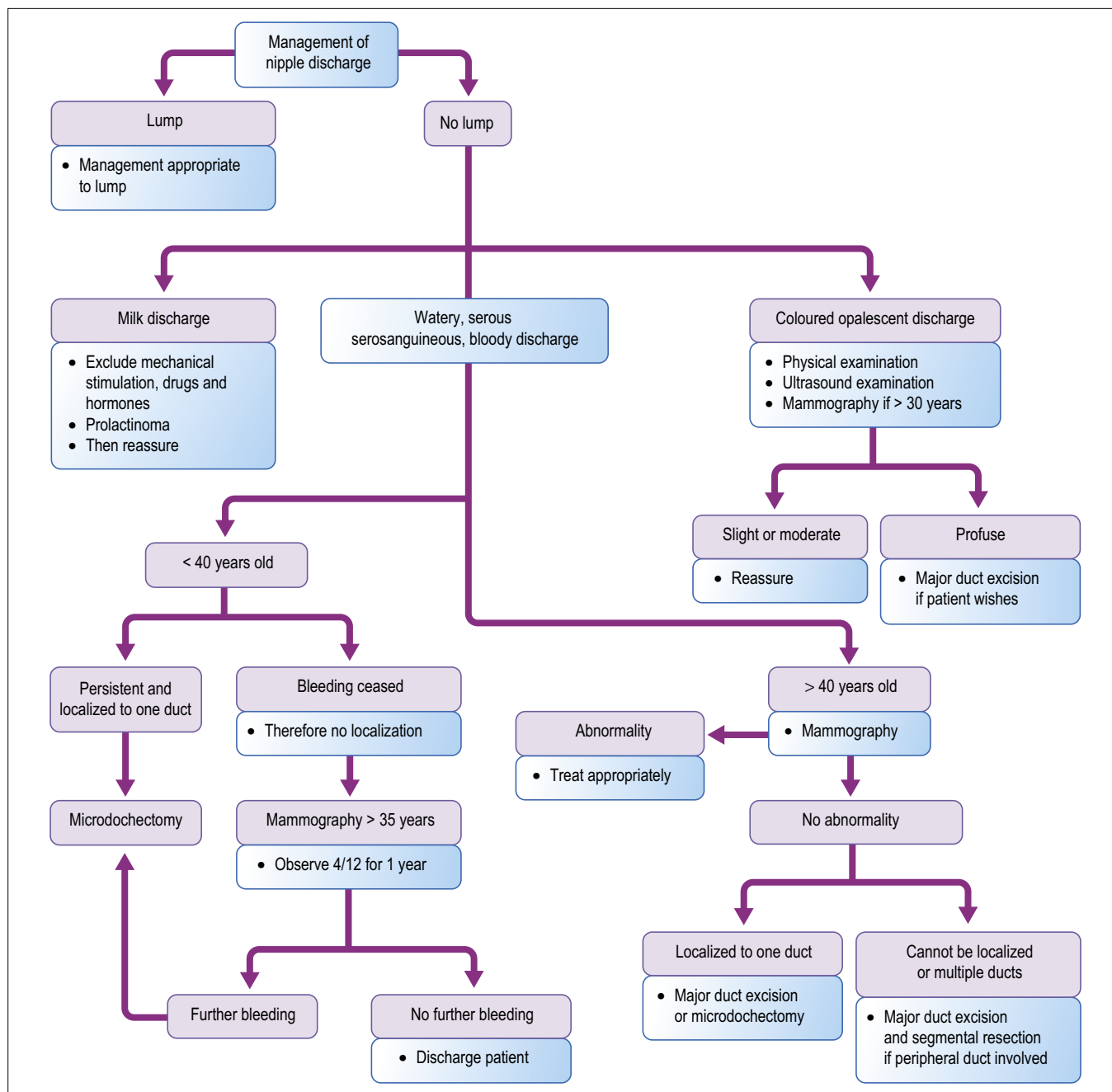


Fig. 13.9 Management of nipple discharge.

Galactorrhoea

The management is that of the underlying cause. Prolactinomas are treated by bromocriptine or cabergolamine, or surgical excision. For drug-induced galactorrhoea, an alternative medication is usually available if the galactorrhoea remains unacceptable. In cases of physiological

discharge, reassurance and cessation of mechanical stimulation should prove sufficient.

Follow-up

Patients who prove to have solitary duct papilloma have insufficient increase in the risk of subsequent

malignancy to justify routine follow-up. Patients with multiple papillomas, or where cytological atypia has been found, do have an increased risk⁷⁷ and should be kept under review. Because the risk is small, long-term and affecting both breasts, long-term follow-up is more appropriate than prophylactic mastectomy.

Carty et al.⁷⁸ followed a small mixed series of patients with mainly non-blood-related discharge for 5 years and showed that the discharge had resolved spontaneously in three-quarters of the women in that period.

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