

THE SIGNIFICANCE OF NIPPLE DISCHARGE*

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TWENTY YEARS AGO Adair¹ wrote: "There are few clinical problems which present such a wide divergence of opinion as the subject of the bleeding nipple." In the succeeding years, little has been accomplished toward unifying opinion on this subject. Especially controversial is the treatment of patients with nipple discharge, and recommendations vary from that of Stowers² "The surgical procedure of choice for all cases of bleeding or discharge from the nipple is a mastectomy," to that of Bartlett³ "bleeding is a positive sign of benignancy and the treatment is always local." It is our belief that the truth lies somewhere between these extreme views, and that if the sources of nipple discharge were more clearly determined, patients would be treated individually rather than according to any routine plan.

Two years ago, in studying a small series of breast lesions,⁴ we noted that only in a small percentage of the patients with a bloody nipple discharge was the discharge caused by a solitary intraductal papilloma; the majority of discharges were associated with multiple gross or microscopic papillomas (papillomatosis) or with other lesions, both benign and malignant.

To verify this conclusion and to secure further information about the disputed problem of nipple discharge we extended the study to include a larger sample of breast cases, covering the six year period from September, 1942, to September, 1948. We reviewed all breast lesions removed

during this period by the staff of the General Surgical Service of the Hospital of the University of Pennsylvania and studied in its Laboratory of Surgical Pathology.

Of a total of 1048 specimens, 97 (or 9.3 per cent) had been associated with nipple discharge. The hospital records of these patients and the pathologic specimens have been analyzed in detail.

The results of this second and larger study verify the conclusions of the previous report. Solitary intraductal papillomas are only rarely a cause of nipple discharge: only five such instances were found in this group of 97 patients. By far the most common lesion associated with nipple discharge is papillomatosis (multiple gross and/or microscopic papillomas). Carcinoma is a not infrequent and, of course, a highly important cause of nipple discharge. An unexpectedly large proportion of discharging nipples result from a group of chronic inflammatory lesions whose common denominator is duct stasis.

ANALYSIS OF DATA

Final Pathologic Diagnosis of 1048 Breast Lesions. The entire series of 1048 breast lesions on which this study is based is presented in Table I according to the final pathologic diagnosis. Approximately one third of the specimens were diagnosed as carcinoma, and slightly less than one fifth as benign neoplasms. The most common pathologic diagnosis was chronic cystic mastitis (37 per cent), but for the purposes of this study we have divided chronic cystic mas-

* Submitted for publication August, 1950.

titis into cases *with* and *without* proliferative change, and have included the former under the group "papillomatosis." Because intraductal papillary proliferation appears to be the factor in cystic disease most influ-

Cause of Nipple Discharge. The number of discharging nipples in this series of 1048 lesions was 97 (9.3 per cent), slightly higher than in our previous study of a small group of breast lesions, but entirely in keeping with the percentages reported in the literature.^{5, 6}

TABLE I.—*Pathologic Diagnoses of 1048 Consecutive Breast Lesions Examined During the Period 1942 to 1948.*

Total specimens examined.....1048		
Total patients.....990		
Pathologic Diagnosis	Number	Per Cent
1. Papillomatosis.....	146	14
a. Without associated chronic cystic mastitis.....	32	
b. With associated chronic cystic mastitis.....	114	
2. Chronic cystic mastitis.....	269	26
Without significant papillary proliferation		
3. Benign neoplasms.....	191	18
Fibro-adenoma.....	176	
Lipoma.....	14	
Leiomyoma.....	1	
4. Inflammatory lesions.....	42	4
Chronic mastitis.....	16	
Granuloma.....	1	
Tuberculosis.....	3	
Fat necrosis.....	9	
Abscess.....	12	
Acute mastitis.....	1	
5. Carcinoma.....	361	34
6. Other malignant neoplasms.....	8	1
Adenofibrosarcoma.....	3	
Fibrosarcoma.....	3	
Liposarcoma.....	1	
Malignant melanoma (metastatic).....	1	
7. Lesions of male breast.....	28	3
a. Hypertrophy.....	26	
b. Carcinoma.....	2	
8. Miscellaneous.....	3	..
Hypertrophy.....	1	
Normal breast.....	1	
Dermatitis of nipple.....	1	
Total.....	1048	100%

The sources of nipple discharge, as determined by the pathologic diagnosis of the 97 breast lesions, are shown in Table II. Papillary proliferation in the ducts (papillomatosis) accounted for the discharge in 46 instances (47 per cent of the total). Yet among these 46 cases there were only five solitary papillomas, as determined by careful gross and microscopic pathologic examination. This observation is of considerable importance to the surgeon because it indicates that the removal of a "solitary papilloma" rarely removes the entire disease. Papillomata were demonstrated grossly in only 22 (48 per cent) of these 46 cases; in the remaining instances the papillomata were too small to be noted except on microscopic study.

Chronic cystic mastitis was a frequent cause of nipple discharge, especially when it was associated with papillary proliferation in the ducts. Chronic cystic mastitis *without* proliferative changes was diagnosed in 9 per cent of the breasts with discharge, and chronic cystic mastitis *with* proliferative changes accounted for 19 per cent of all instances of nipple discharge.

One of the major findings of the study was that chronic inflammatory lesions caused the discharge in 13 per cent of the patients. While most of these breasts with inflammatory reactions had a non-bloody discharge, three had discharges that were distinctly bloody, indicating that the type of discharge is not a reliable criterion for diagnosis of the underlying pathologic lesion. The initiating factor in the chronic inflammatory lesions appeared to be duct stasis with accumulation of cellular detritus and much lipid material. This process progressed to varying degrees and types of in-

ential in causing nipple discharge, it seemed logical to place all cases with papillary duct hyperplasia in one group. The remaining instances of chronic cystic mastitis are grouped separately as "chronic cystic mastitis without significant papillary proliferation." We have attempted to exclude simple ductal hyperplasia from the group of papillomatous lesions, but we recognize that the distinction is necessarily arbitrary and artificial.

flammatory reaction, producing lesions that might readily be classified under a number of diagnostic and descriptive terms to be found in the literature: periductal mastitis, comedomastitis, plasma cell mastitis, and fat necrosis. Identical changes were found in many of the breasts in which papillomatosis, carcinoma, and even occasionally chronic cystic mastitis were the primary lesions.

in which it was diagnosed. Nearly a third of the breasts with chronic inflammatory lesions were associated with nipple discharge. On the other hand only 7 per cent of the carcinomas resulted in a discharge of any kind. Grouping all benign lesions together we find that the incidence of discharge in benign lesions is 11 per cent as compared to the incidence of 7 per cent

TABLE II.—*Pathologic Lesions Associated with Nipple Discharge; 97 Breasts.*

Pathologic Lesion	Number of Breasts With discharge	Percent
1. Papillomatosis.....	46	47.4
a. Solitary papillomas.....	5	5.2
b. Multiple gross and microscopic papillomas.....	17	17.5
c. Multiple microscopic papillomas.....	24	24.7
(19, or 41 percent of these lesions were associated with chronic cystic mastitis)		
2. Chronic cystic mastitis without significant papillary proliferation.....	9	9.3
3. Chronic inflammatory lesions...	13	13.4
4. Carcinoma.....	24	24.7
5. Lesions of male breast.....	2	2.1
6. Miscellaneous.....	3	3.1
Total.....	97	100.0

TABLE III.—*Incidence of Nipple Discharge in Various Types of Breast Lesions.*

Pathologic Diagnosis	Total Number of Breasts	Number With Discharging Nipples	Percent
1. Papillomatosis.....	146	46	31
Without assoc. C. C. M.	(32)	(19)	(59)
With assoc. C. C. M.	(114)	(27)	(24)
2. Chronic cystic mastitis... without significant papillary proliferation	269	9	3
3. Benign neoplasms.....	191	0	0
4. Chronic inflammatory lesions.....	42	13	31
5. Carcinoma.....	361	24	7
6. Other malignant neoplasms.....	8	0	0
7. Lesions of the male breast	28	2	7
8. Miscellaneous.....	3	3	..
Total.....	1048	97	9.3

One fourth²⁴ of the discharges were produced by carcinoma. The carcinoma was associated with a palpable mass in all but two instances, and both of these exceptions proved to be cases with Paget's disease of the nipple. Fifteen of the carcinomas were predominantly intraductal; seven of the 15 also exhibited invasive growth. Of the 15 intraductal carcinomas, seven were associated with the nipple changes of Paget's disease.

The frequency with which any particular breast lesion produced nipple discharge is more clearly illustrated by Table III, which shows the incidence of discharge for each pathologic diagnosis in this series of 1048 lesions. Papillomatosis resulted in nipple discharge in nearly a third of the breasts

for malignant lesions. Thus in our series the association of discharge with a breast lesion that is operated on was a differential point slightly favoring benignancy.

Type of Nipple Discharge. The type of nipple discharge in the 97 breasts was determined clinically and the results are shown in Table IV according to the pathologic diagnosis. (Microscopic examinations of the discharges were made in only a few instances.) All types of discharges were found in association with all types of lesions, and although there was some concentration in the number of bloody and serosanguineous discharges in the presence of papillomatosis and carcinoma, non-bloody discharges were also present in these groups. Nine of the 46 breasts with papillomatosis had non-bloody discharge, and seven of the 24 carcinomas had non-bloody discharge. It is clear that a

non-bloody discharge does not rule out the possibility of a malignant or premalignant lesion.

Age. The average age of the patients with discharge, listed according to the major pathologic diagnosis, is seen in Table V. It is apparent that proliferative changes predominate in the menopausal and postmeno-

microscopic dimensions in almost half of the cases. Figure 1 shows the earliest manifestations of intraductal papillary growth, both A and B occurring in the same duct. Figure 2 is a photomicrograph of a typical, fully developed, intraductal papilloma and Figure 3 illustrates three variants: (A) a more or less solidly cellular papilloma with little stroma, still entirely benign; (B) a

TABLE IV.—*Clinical Appearance of Nipple Discharge in 97 Breasts.*

Pathologic Diag.	Total	Sero-			
		Bloody	Sang.	Serous	Other
Inflammatory lesions....	13	3	1	5	4
Chronic cystic mastitis..	9	4	0	3	2
Papillomatosis.....	46	26	11	6	3
Carcinoma.....	24	11	6	5	2
Miscellaneous.....	5	2	1	2	0
Total.....	97	46	19	21	11

TABLE V.—*Average Age According to Final Pathologic Diagnosis of 97 Bleeding Nipples.*

Diagnosis	Average Age
Chronic cystic mastitis.....	35
Chronic inflammatory lesions.....	40
Papillomatosis without chronic cystic mastitis....	41
Papillomatosis with chronic cystic mastitis.....	46
Carcinoma.....	54
(Average age of patients with benign lesions....)	42)

pausal years. Benign lesions occur primarily in the younger age groups (average age 42 years). The greater average age (54 years) of the patients with carcinoma and associated nipple discharge points to the more ominous significance of this symptom when

papilloma with extensive hyalinization; and (C) a papilloma composed in large part of apocrine cells.

The occurrence of nipple discharge in 13 per cent of the present series in association with no specific lesion other than duct stasis

TABLE VI.—*Incidence of Stasis, Distention, and Inflammation in Cases of Papillomatosis, Chronic Cystic Mastitis, and Carcinoma Associated with Nipple Discharge.*

Primary Diagnosis	Number Cases	Stasis and Distention	Inflammation		
			Slight	Moderate**	Marked†
Papillomatosis.....	45*	35	11	14	4
Chronic cystic mastitis.....	9	3	2	1	..
Without significant proliferation					
Carcinoma.....	17‡	9	..	7	2

* In the case of one solitary papilloma, insufficient material was available for study of the mammary tissue.
 ** Occasionally showing small foci of fat necrosis.
 † Including more extensive fat necrosis in every case.
 ‡ In only 17 of the 26 carcinomas were adequate sections of noncancerous breast tissue available for study.

it is encountered in patients in the usual "cancer age range," whether or not a mass is palpable. Seventy per cent of the patients over 60 years of age with nipple discharge had carcinoma.

PATHOLOGIC ASPECTS

The pathologic features of intraductal papillomas are well known and the cases studied in this series illustrate all variations. It is striking that the papillomas were of

and distention, with varying kinds and degrees of secondary inflammatory change, was of great interest. Figure 4A illustrates an early change in this sequence: distention and stasis, largely of lipoid material, and some periductal inflammation and fibrosis.

Subsequent stages of the developing inflammatory reaction are illustrated in Figures 4B, 4C, 5 and 6. In various portions of the tissue from the breasts of this group, one may see changes consistent with the

histopathologic pictures designated as fat necrosis⁷ (Fig. 4B and 4C), comedomas-titis⁸ (Fig. 6A), and plasma cell mastitis⁹⁻¹¹ (Fig. 6B). These varying pictures were at

In none of the cases grouped above under the heading of "chronic inflammatory lesions" was an anatomical basis for ductal obstruction demonstrated. Yet many of the

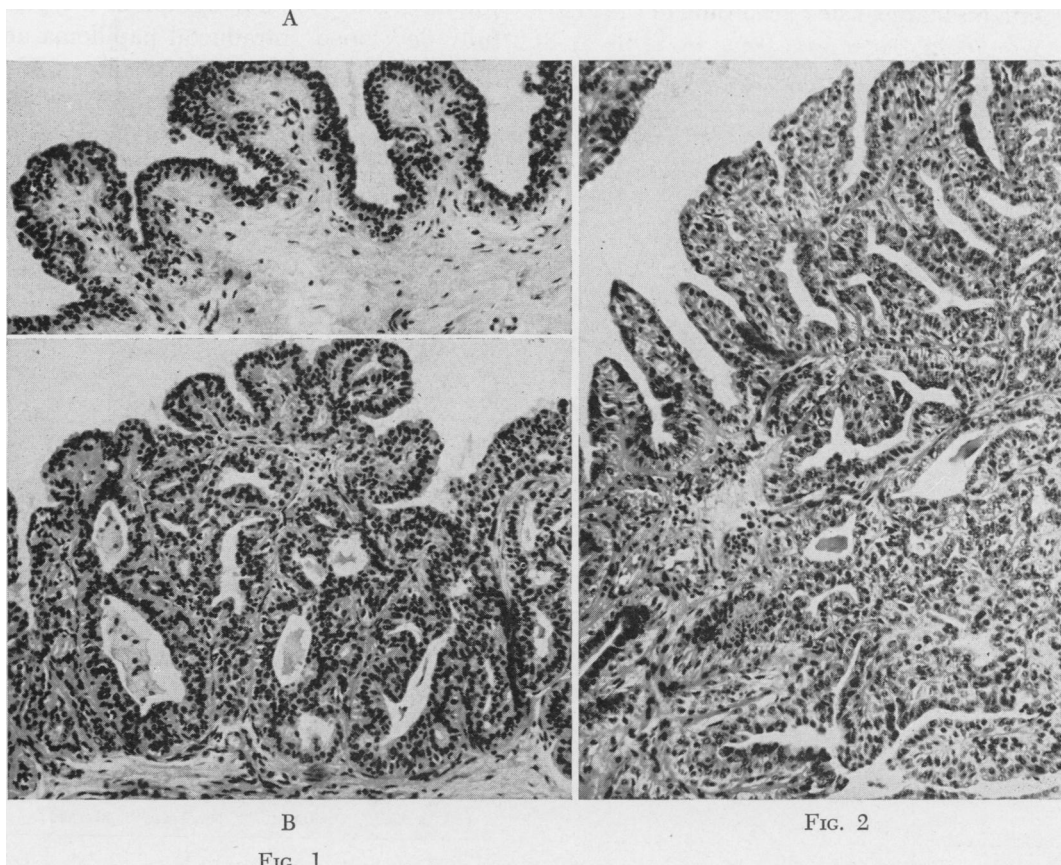


FIG. 1.—(A) shows early papillomatous intraductal proliferation, (B) more complex vascularized papillomatosis. The photomicrographs have been made from opposing walls of the same duct. Hematoxylin and eosin, x 120.

FIG. 2.—Portion of a classical, bleeding intraductal papilloma 9 mm. in diameter. Hematoxylin and eosin, x 130.

times seen in different portions of single specimens. That the inflammatory lesions designated by these various diagnostic terms all represent variants of the same fundamental process and that they are dependent upon primary ductal stasis and distention has been pointed out before.^{10, 12} Fat necrosis was a conspicuous figure in five of the 13 cases in this group and three cases might readily be classified as plasma cell mastitis.

breasts classified under other primary diagnoses showed changes that were identical in quality and often comparable in quantity. Foote and Stewart¹² have pointed out the occurrence of these static and inflammatory changes both with and without a demonstrable anatomic basis for ductal obstruction. The incidence of stasis, distention, and resulting inflammation in the various diagnostic categories is detailed in Table VI. The usual explanation for the bleeding as-

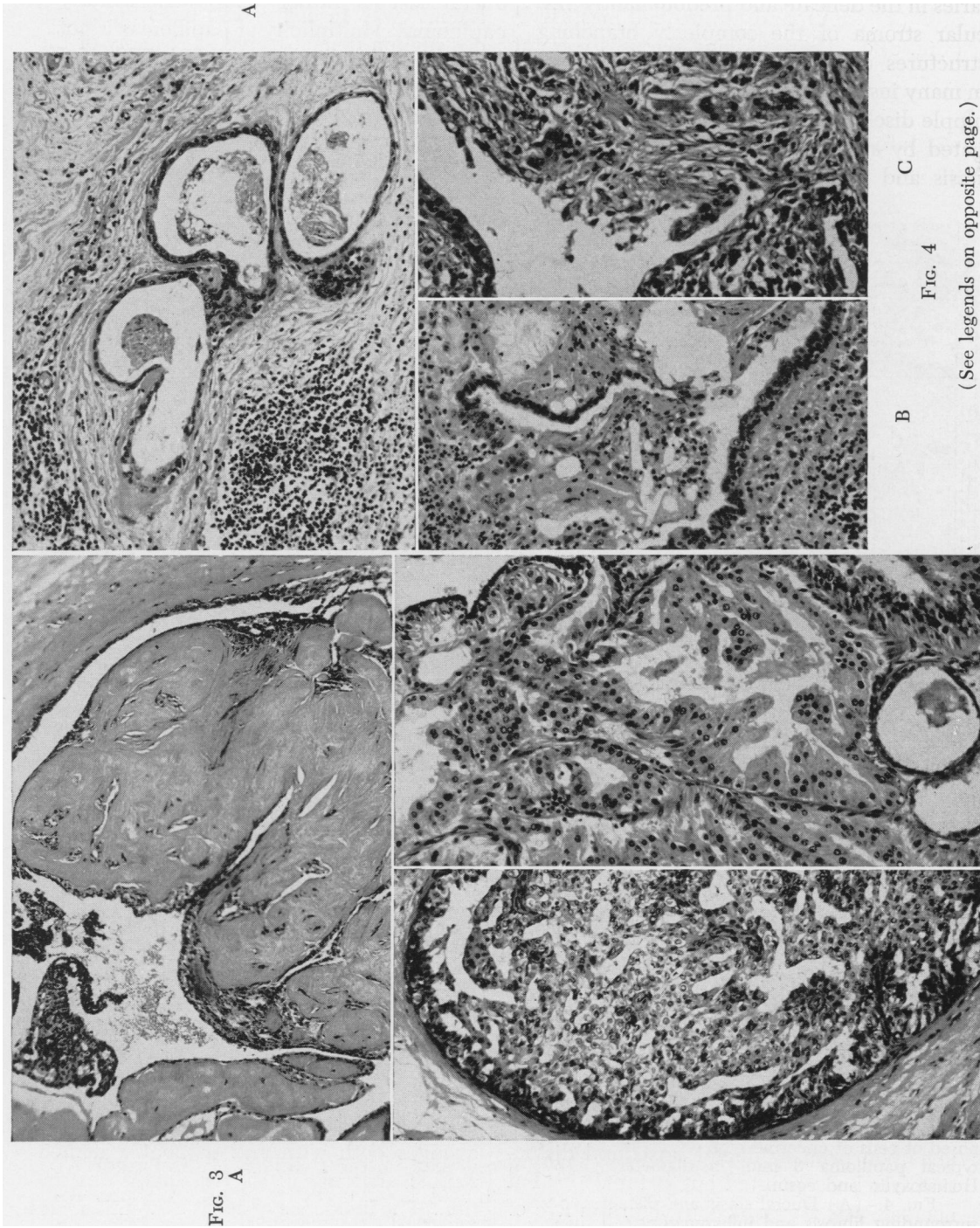


FIG. 3
A

FIG. 4
B C
(See legends on opposite page.)

sociated with papillomas—rupture of capillaries in the delicate and predominantly vascular stroma of the complexly branching structures (Fig. 2) is undoubtedly correct in many instances, but the high incidence of nipple discharge associated with lesions initiated by stasis, and the high incidence of stasis and resulting inflammatory changes

discharge is associated with multiple intraductal lesions rather than with solitary papillomas. Multiplicity of papillomas is not a new concept. Recent reports emphasize multiplicity: Hinchey⁵ found papillomas to be multiple in 30 per cent of his cases; Estes and Phillips¹³ in 21.7 per cent; and Donnelly¹⁴ in 20 per cent. We, however, found

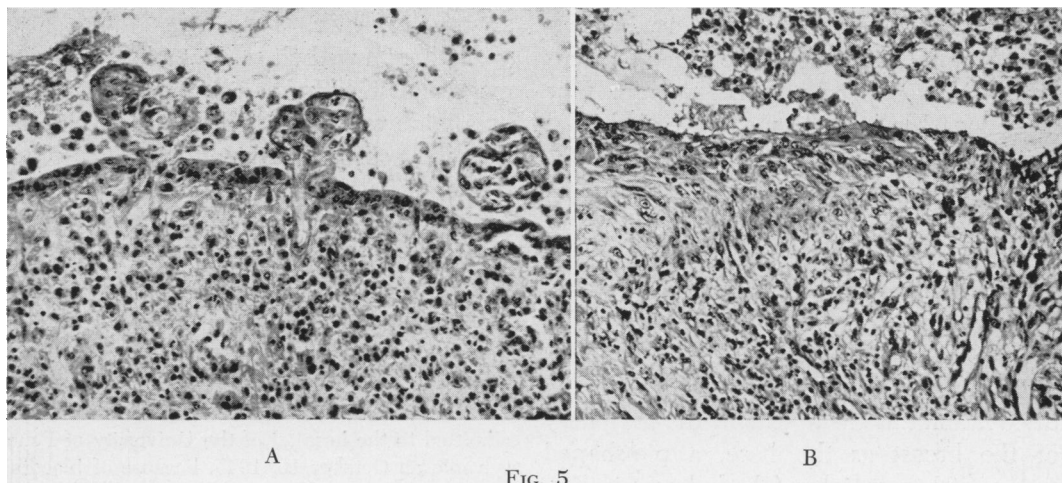


FIG. 5.—Inflammatory reaction in duct wall. (A) Tiny granulomata projecting into lumen through breaks in continuity of epithelial layer; (B) squamous metaplasia of duct lining. Hematoxylin and eosin, x 135.

in breasts bearing intraductal papillomas and carcinomas suggests that in many breasts, especially those that do not contain classical bleeding papillomas, the discharge may be dependent upon ductal obstruction and the associated inflammation.

DISCUSSION

A striking fact demonstrated by this study is the frequency with which nipple

FIG. 3.—Variations encountered in the histologic appearance of intraductal papillomas. (A) Extensive hyalinization (x 70); (B) partly solid and partly papillary hyperplasia with vascularization at only a few points (x 120); (C) area composed of cells of apocrine type within an otherwise typical papilloma 6 mm. in diameter (x 120). Hematoxylin and eosin.

FIG. 4.—(A) Ductal stasis and distention with surrounding fibrosis and inflammatory cell infiltration (x 120). (B and C) Destruction of portions of ductal lining epithelium with inflammation and foreign body reaction to lipid debris—"fat necrosis." Note cholesterol crystal clefts (B, x 120; C, x 155). Hematoxylin and eosin.

multiplicity in a much higher percentage than reported in the literature. Of 46 instances of significant papillary ductal proliferation (papillomatosis), only five were solitary papillomas; the remaining 41 or 89 per cent, had multiple lesions.

In view of the large number of multiple papillomas, one might expect that in this series mastectomy would have been the usual operation performed for papillomatosis. Yet mastectomy was rarely used in this group of patients. Does the frequent multiplicity of the lesions in papillomatosis mean that the entire breast should always be removed for the symptom of discharge? We do not believe that it does. A significant number of discharges are due to other benign lesions, such as chronic inflammation dependent upon duct stasis, and chronic cystic mastitis without papillomatosis. The

wholesale removal of entire breasts for these benign lesions would be unfortunate. Indeed, the majority of mammary lesions associated with discharge are benign.

It is our belief that all nipple discharges not accounted for by the physiologic changes of pregnancy or lactation should be investigated surgically and pathologically. In those instances due to papillomatosis the lesions are usually multiple and a wide segment of the breast should be removed, centering on the duct or ducts involved. Our procedure has been to make a "T" shaped incision with the short arm of the "T" slightly curved and placed within the areola and the long arm extending to the periphery of the breast over the duct segment from which discharge has been expressed (Fig. 9). The areolar flap is dissected back to the nipple and the involved duct or ducts divided just beneath the nipple. With the divided duct as the apex and the periphery of the breast as the base, a pie-shaped wedge of breast tissue (shaded area in Fig. 9) is excised. This procedure is intended to remove the diseased lacteal duct with all its tributaries, where the additional papillomas may be expected to occur with greatest frequency.

If multiple papillomas are found on careful gross and microscopic examination of the excised segment should the entire breast then be removed? Follow-up data relative to this problem are not yet available in our series. The follow-up data of Wakely¹⁵ and Estes and Phillips¹³ failed to prove subsequent development of carcinoma following the local excision of a papilloma. Estes and Phillips noted, however, that 11.7 per cent of the patients who had local excisions for papillomas later needed further breast surgery for benign lesions, chiefly additional papillomas. Since the mortality and morbidity of a simple mastectomy are almost negligible, the argument against mastectomy centers on the psychic effect on the patient of the removal of her

breast. Reactions vary tremendously from patient to patient, and psychic factors must be carefully weighed in the decision as to treatment. A young woman (especially unmarried) would be more justified in taking the risk of local excision than a woman past the menopause, for whom the loss of a breast should not produce great mental trauma, and whose chances of having cancer are much greater.

Although we believe that a local excision may be justified for papillomatosis this must be a wide wedge-shaped excision including the entire segment drained by the involved duct and its tributaries from the periphery of the breast to the nipple (Fig. 9). Failure to include the entire duct segment had unfortunate results in the following patient included in this series.

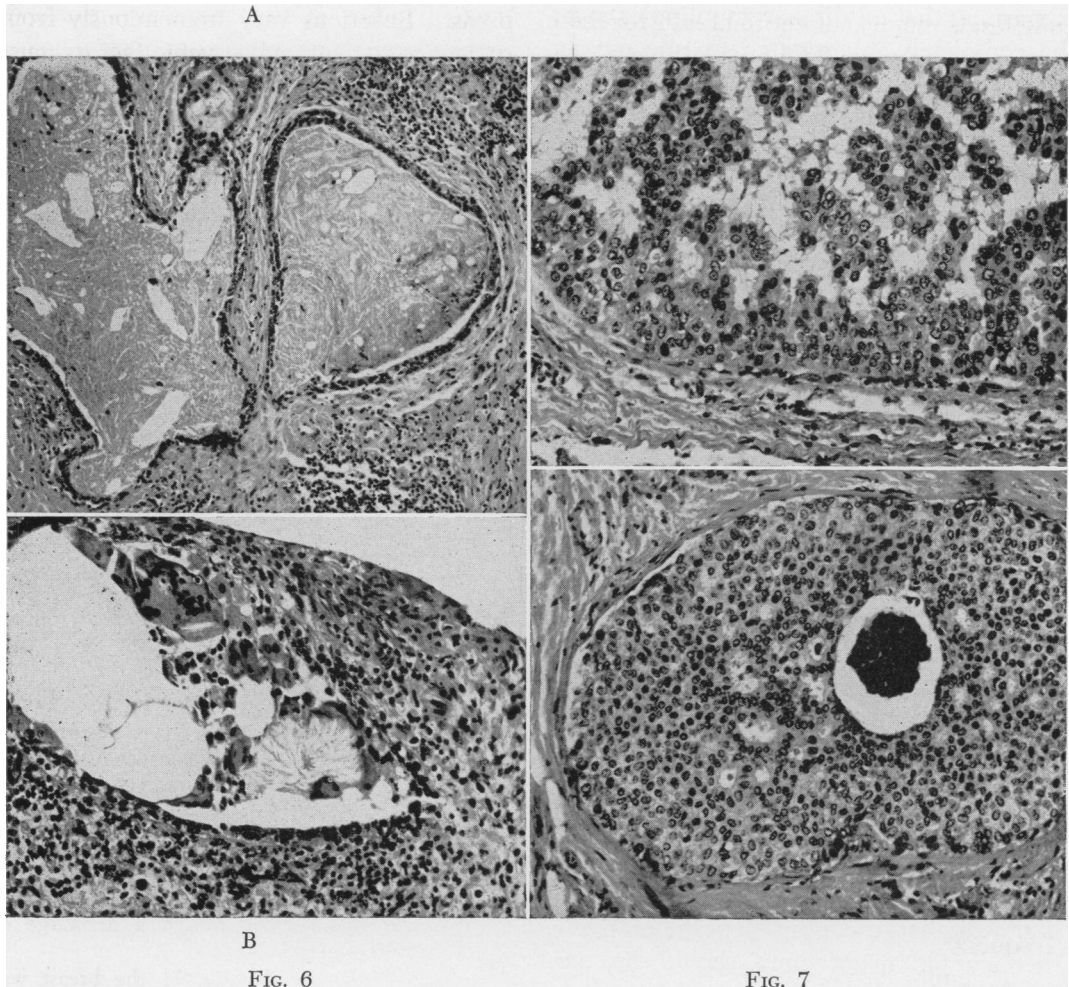
CASE REPORT

D. A., a 57-year-old Negro housewife, was admitted to the hospital of the University of Pennsylvania on October 10, 1945, because of bleeding from the right nipple of six weeks duration. The discharge had varied in character from sero-sanguineous to bright red.

On physical examination no masses could be felt in either breast. Pressure just caudad to the right areola at 7 o'clock caused a discharge of blood from the nipple.

At operation on October 11 the breast was explored in the area where pressure caused a discharge. Dilated ducts were exposed and a limited local excision performed. No gross papillomas were seen, and on microscopic examination only a few tiny intraductal papillomas were observed. It did not seem certain that these accounted for her bleeding. No further surgical procedure was done.

Six months after operation, the patient first noted a mass in the right breast just peripheral to the scar of the previous operation. She was not seen in follow-up clinic until six months after noting this mass and was then immediately admitted to the hospital. A firm mass measuring about 2 cm. x 1 cm. just below and lateral to the old scar was excised at operation on November 25, 1946. The mass proved to be a large cystic dilation of ducts containing old blood. Adjacent to the wall of this cystic cavity was a firm tumor, 1 cm. in diameter, which on quick frozen section examination proved to be carcinoma. Radical mastectomy was performed. Subsequent pathologic



B

FIG. 6

FIG. 7

FIG. 6.—Chronic mastitis. (A) Distention of ducts. Such ducts may be grossly apparent and their contained detritus may be readily expressed—“comedomastitis” (x 90). (B) Inflammatory reaction within duct wall. The predominant cell is the plasma cell. Note crystalline debris (x 150). Hematoxylin and eosin.

FIG. 7.—Intraductal carcinoma. Sections made following radical mastectomy in the case reported in the text. Invasive growth was demonstrated in other sections. Hematoxylin and eosin, x 150.

study showed the carcinoma to be largely intraductal (Fig. 7), but with definite stromal invasion. One of 32 axillary nodes contained metastatic tumor.

Upon restudy of the original material, the proliferative changes were considered to be cytologically atypical (Fig. 8), a fact that should have been noted and utilized originally as an indication for more extensive surgery. There seems to be no way of deciding whether the lesion which produced the original bleeding was a cancer at that time or was still a benign, although precancerous,

hyperplasia. Had a wedge designed to include the entire duct segment been excised, the lesion would have been removed and diagnosed at the time of the first operation.

Discharge due to carcinoma is usually associated with a mass, which is best managed by excision biopsy for diagnosis followed by radical mastectomy when the diagnosis is confirmed. The fact that two of our patients with carcinoma and nipple discharge did not have a mass, however, is

a warning that all discharging nipples must be completely investigated to rule out an occult carcinoma.

At times, simple mastectomy may be the treatment of choice for discharge from the nipple. If the involved segment cannot be located preoperatively (it *could* be located in the great majority of our patients) and no dominant lump is present, if multiple nipple ducts are proved to be involved, or

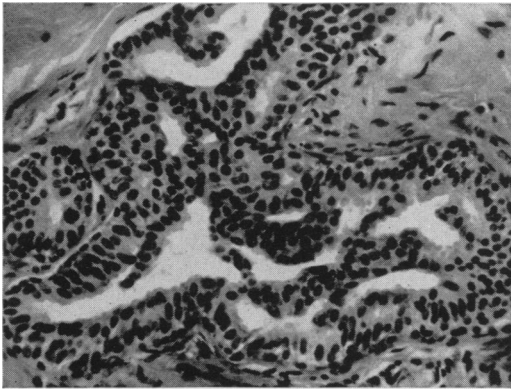


FIG. 8.—Cytologically atypical intraductal hyperplasia noted one year prior to the detection of cancer and radical mastectomy in the case reported in the text. Hematoxylin and eosin, x 195.

if the discharge continues postoperatively, then simple mastectomy should be performed. Regular follow-up examinations are absolutely essential in those patients who have a procedure less than mastectomy for nipple discharge.

This study does not contribute to the unsettled question of the cancerous potentialities of the intraductal papilloma. We have been able to identify cytologic atypicalities in the papillomas and papillary hyperplasias of only six breasts in this series. In five of these, fully developed malignant change was already present and readily recognized. Foote and Stewart¹² who have described these changes in detail, noted them frequently in association with cancer but rarely in non-cancerous breasts. The sixth instance in which we recognized atypical proliferation was in the case reported above,

in which radical mastectomy was performed for carcinoma one year after partial mastectomy for the symptom of nipple discharge. Restudy of the pathologic material from the first operation confirmed the observation that papillomatous changes were minimal—possibly too slight to account for bloody discharge; but in addition, it was apparent that the microscopic papillomas were cytologically atypical (Fig. 8).

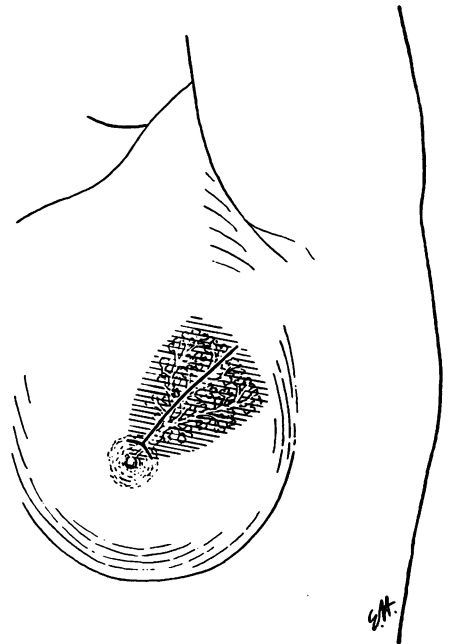


FIG. 9.—Incision used to remove an involved duct with its tributaries. The shaded area is excised.

Since, with the exception of this case, we have observed such atypicalities only in cancerous breasts, and since Foote and Stewart¹² found them most frequently in cancerous breasts, we raise the question whether cancer might not have been present at the time of the first operation, although not included in the tissue removed by the surgeon. Certainly atypical, hyperplastic intraductal changes must be considered an ominous sign. At the very least, they represent definite precancerous change, but, more often than not, they serve as an

indication that intraductal carcinoma is to be found elsewhere in the same breast.

SUMMARY

The clinical and pathologic data relating to 97 female breasts operated upon for the symptom of nipple discharge have been analyzed. The primary lesion in 47 per cent of the cases was intraductal papillomatosis, with or without other changes of chronic cystic mastitis. Solitary intraductal papillomas, without additional gross or microscopic tumors, were encountered only five times in this series. Carcinoma was the primary disease in 25 per cent and was usually wholly or largely intraductal: chronic cystic mastitis without significant intraductal papillary proliferation was noted in 9 per cent and a variety of inflammatory lesions dependent upon ductal stasis and distension comprised 13 per cent. Similar static and inflammatory changes were often found in association with papillomatosis and carcinoma. The type of discharge, in particular whether or not it was bloody, was not a reliable diagnostic aid.

In a majority of cases presenting with the symptom of nipple discharge, the source of the discharge could be localized to a single duct or duct system. In such cases, it is considered that resection of that segment of the breast drained by the offending duct or duct system constitutes adequate treatment. This is the minimum operative procedure that should be performed. Because of the 25 per cent incidence of carcinoma as a cause of nipple discharge, we believe that all nipple discharges should be thoroughly investigated both surgically and pathologically, regardless of the type of

discharge and the presence or absence of a palpable mass.

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