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Immunoglobulins and Secretory Component in Endometrium and Cervix

Influence of Inflammation and Carcinoma*

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Summary. The synthesis of immunoglobulins and secretory component in the cervix and the endometrium was studied by tissue culture and immunofluorescence. Out of the 75 cervical biopsies studied, 17 were epidermoid carcinomas, 8 were carcinomas in situ and 23 tissues had inflammatory or metaplastic lesions. A total of 49 samples from endometrium were studied, out of which 22 were in the proliferative phase, 17 were in the secretory phase and 4 were carcinomas. In the cervical tissues without lesions, there were very few plasmacytes, the synthesis of immunoglobulins was low and in 66% of the tissues the synthesis of IgG was equal to or higher than that of IgA. With local modifications, the IgG synthesis was even more preponderant and was very important in epidermoid carcinomas which were infiltrated with numerous IgG plasmacytes. Secretory component was synthesized by almost all the tissues except the epidermoid carcinomas. The endometrium did not synthesize immunoglobulins; secretory component was synthesized only by endometrial tissue in the secretory phase and by 2 of the 4 carcinomas studied. It seems that in the cervix and the endometrium there is no relationship between the production of secretory component and the presence of IgA plasmacytes which probably localise as a result of other influences. The conditions in which the local secretory immunological system would react preferentially remain to be determined.

Key words: Secretory component – Immunoglobulins – Cervix uteri – Endometrium – Cervix neoplasm.

Introduction

The female genital tract is capable of producing specific antibodies following local immunization and these antibodies are partly of the secretory IgA class

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(Strauss, 1961; Waldman et al., 1971; Waldman et al., 1972; Ogra and Ogra, 1973). It seems likely therefore, that the female genital tract belongs to the secretory immunological system although all of the criteria which define the secretory immunological system are not always present, and some observations are incompatible with this conclusion. Vaginal secretions may contain antibodies, essentially of the IgG class, which originate from serum by transudation (Chodirker and Tomasi, 1963; Masson et al., 1969). There is some disagreement concerning the number of IgA plasmacytes present in the female genital tract, particularly in the cervix (Lippes et al., 1970; Tourville et al., 1970; Hutcheson et al., 1974; Rebello et al., 1975). Reports of the failure of local immunizations have been made (Vaerman and Ferin, 1973).

The repercussions of a carcinoma on the local secretory immunological system have been described for both carcinomas of the breast and the digestive system (Waldman et al., 1970; Levy et al., 1975; Logerfo and McLanahan, 1976; Weisz-Carrington et al., 1976). No such observations have been made on carcinomas of the cervix. The aim of the present work has been to evaluate the synthesis of immunoglobulins, C'3 and secretory component in human cervical mucosa and endometrium. Samples of endometrium in the secretory or the proliferative phase and samples of cervical mucosa with or without various lesions have been selected. We have attempted to correlate the synthesis of these different proteins with the morphology of the tissues. Two techniques were used for this study; immunofluorescence and in vitro incorporation of labeled amino acids into proteins.

Materials and Methods

Cervical Tissues. A total of 75 samples of cervical tissues from 75 patients were obtained immediately after surgery. These included 27 cervical tissues without lesion, 12 with chronic inflammation, 11 with epithelial metaplasia without significant inflammation, 8 with carcinoma-in-situ and 17 with epidermoid carcinoma.

Endometrial Tissues. A total of 49 samples were obtained immediately after surgery. Of these endometrial tissues, 17 were in the secretory phase, 22 were in the proliferative phase, 6 were in the inactive phase and 4 were carcinomas (3 adenocarcinomas and 1 adenosquamous tumor).

Antigens. Human milk was obtained from the Department of Gynecology and Obstetrics, University of Lausanne. Secretory IgA was isolated from human milk (Tomasi et al., 1965) and free secretory component was prepared from the milk by the method of Brandtzaeg (1974a). C'3 was a gift from Dr. Jacot-Guillarmod, Lausanne, Switzerland.

Antisera. Antisera against free secretory component (SC), secretory IgA (S IgA) and C'3 were produced in rabbits weighing 2.5 to 3 kg. The rabbits were immunized i-m each week with 500 μg of protein in 1 ml saline emulsified with an equal part of Freund's complete adjuvant. They were bled one week after the third injection. Antisera against SC and S IgA were absorbed with various proteins from human milk and/or human serum to make them specific. Each of these antisera was tested by immunoelectrophoresis and by double diffusion in agar against human serum and human milk. Antiserum specific for free secretory component gave two lines against lactoserum; one corresponded to lactoferrin, the other to free secretory component and had a cathodal spur corresponding to the bound secretory component. This antiserum was not absorbed further. Antiserum against S IgA gave two lines; the anodal arc corresponded to the free SC whereas the cathodal

arc represented S IgA. The antiserum specific for C'3 gave a single line against human serum. Swine antisera specific for IgG, IgA, IgM and polyvalent against human serum proteins were obtained commercially (Research Institute for Immunology, Prague, Czechoslovakia). The specificity of the antisera to the various immunoglobulins was also tested by immunofluorescence (Hurlimann et al., 1976).

Immunofluorescence. The tissue fragments were washed for 12 h in 0.125 M NaCl:0.025 M phosphate, pH 7.1, fixed in alcohol and embedded in paraffin according to the method of Sainte-Marie (1962). IgG, IgA and IgM were detected on 6 µm tissue sections by the direct immunofluorescence technique. The various antisera were labeled with fluoresceine isothiocyanate (Calbiochem, Los Angeles, Calif.) according to the method of The and Feltkamp (1970), the fluorescein: protein molecular ratio being between 1 and 3. The slides were examined on a Zeiss Universal microscope with incident illumination from an Osram HBO 200-watt high pressure mercury vapor lamp. The filters 2 × KP 500 and BP 525 were used.

Tissue Cultures. About 40 fragments of each tissue sample were explanted in tubes and cultured in a medium containing ^{14}C labeled amino acids according to a technique described previously (Hurlimann et al., 1976).

After the incubation period, the culture fluids were dialyzed against 0.005 M barbital buffer at pH 8.6 for 48 h and lyophilized. The lyophilized powder was dissolved in 0.2 ml of distilled water and the solutions were analyzed by immunoelectrophoresis and autoradiography.

Immunoelectrophoresis. The micromethod of Scheidegger (1955) was used with slight modifications for the LKB apparatus 6800 (LKB Products, Stockholm, Sweden). Concentrated culture fluids were added with a carrier to the antigen well. One µl of normal human serum was used as carrier for the detection of IgG, IgM, IgA and C'3; one µl of lactoserum was used as carrier for detection of free secretory component, lactoferrin and secretory IgA.

Autoradiography. After double diffusion, the immunoelectrophoretic slides were washed with 0.9% NaCl solution, dried, and placed in contact with photographic film (Kodak professional Royal Pan 400 ASA) for 14 days at room temperature. The intensity of the autoradiographic lines was classified from + to + + +.

Results

Cervical Tissues without Lesion

Out of the 26 samples examined by immunofluorescence 9 had no plasmacytes. The others showed very few plasmacytes around the cervical glands and under the surface epithelium. No immunoglobulins were seen in the epithelial cells. The lumen of several glands contained material positive for IgG and IgA.

Out of the 27 samples cultured in vitro, 20 synthesized immunoglobulins, whose synthesis was always low as judged by the intensity of the radioactive lines (Fig. 1B and C). Taking into account the results from the two techniques, which are often concordant, 18 out of the 27 tissues had a local IgG synthesis equal to or higher than the IgA synthesis (Table 1).

Only two samples synthesized IgM in vitro and the same samples showed rare cells positive for IgM when examined by immunofluorescence. The majority of the tissues synthesized C'3 (78%) and secretory component (89%) (Fig. 1A and D).

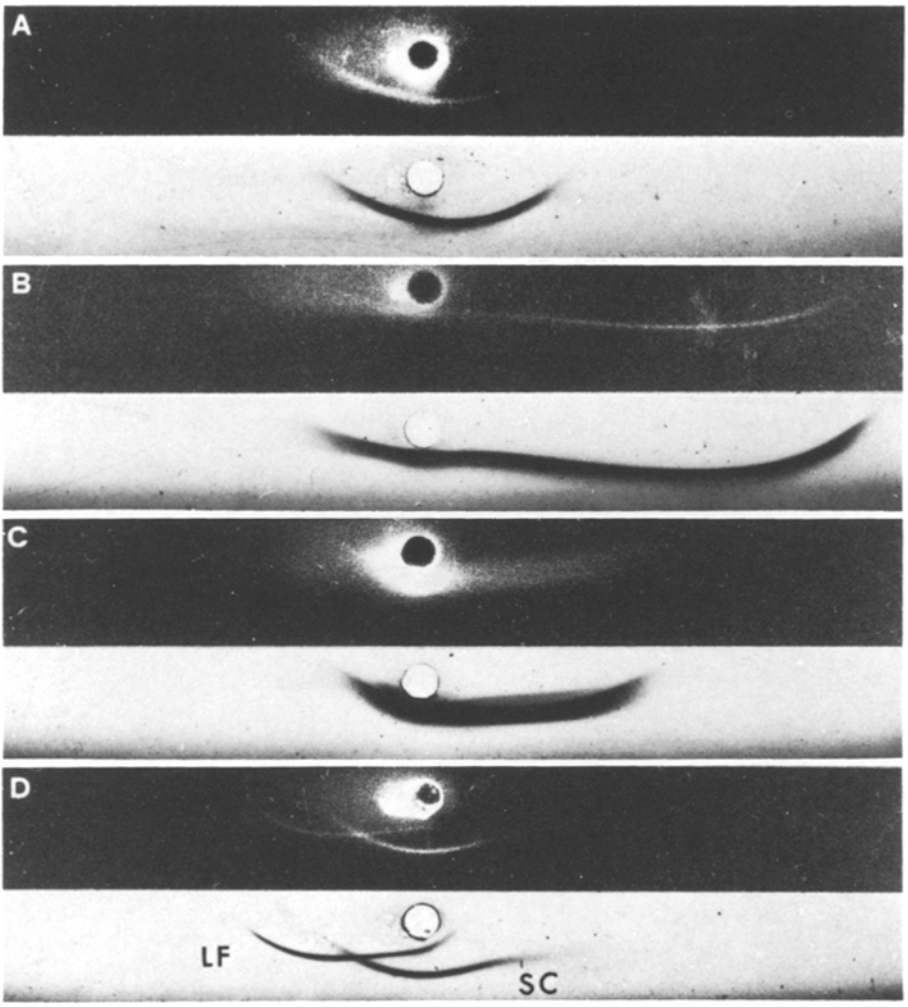

Fig. 1A–D. Autoradiographs of immunoelectrophoresis made with culture fluid from normal cervical tissues. **A** Normal human serum as carrier; antiserum specific for C'3. **B** Normal human serum as carrier; antiserum specific for IgG. **C** Normal human serum as carrier; antiserum specific for IgA. **D** Human milk as carrier; antiserum specific for free secretory component (*SC*). This antiserum also reveals lactoferrin (*LF*). The corresponding stained slide is shown under each autoradiograph

Cervical Tissues with Metaplasia

Out of the 11 samples examined by immunofluorescence, 2 had no plasmacytes, the others showed few of these cells. The 11 samples were also cultured in vitro, immunoglobulin synthesis was detected in 8 culture fluids only and was relatively low. The predominant immunoglobulin class is indicated in Table 1.

Table 1. Synthesis of C'3, IgG, IgA and secretory component by cervical tissues. Results given for IgG and IgA are the summation of in vitro synthesis and immunofluorescence. Results given for C'3 and secretory component are those of in vitro synthesis only

	Immunoglobulins			C'3	Secretory component		
	G	A	O		free SC	free SC+ SIgA	SIgA
Normal (27)	18	7	2	21	9	12	3
Metaplasia (11)	9	0	2	8	3	6	0
Cervicitis (12)	10	0	2	8	2	5	2
Carcinoma in situ (8)	7	1	0	4	1	2	2
Epidermoid carcinoma (17)	17	0	0	6	2	0	0

G = predominance of IgG; A = predominance of IgA; O = absence of immunoglobulins; Numbers of cases are given between parentheses

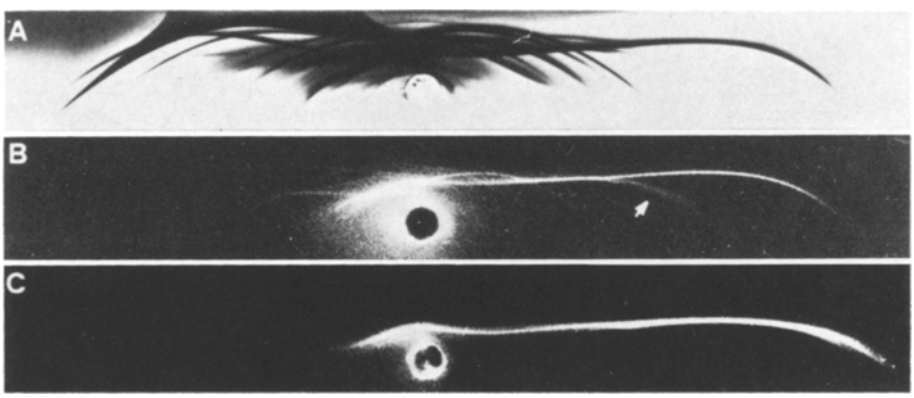

Fig. 2A–C. Autoradiographs of immunoelectrophoresis with normal human serum as carrier and antiserum polyvalent against human serum. **A** Stained slide. **B** Autoradiograph made with culture fluid from cervical tissue with inflammation. The lines of IgG and of IgA (*arrow*) are labeled. **C** Autoradiograph made with culture fluid from epidermoid carcinoma of the cervix. Intense labeling of the IgG line

Cervical Tissues with Inflammation

Eleven samples were examined by immunofluorescence out of which 10 had a marked plasmacytic infiltration. Nine out of these 11 samples synthesized immunoglobulins in vitro and in 7 cases the IgG synthesis was higher than that of IgA (Fig.2B). Eight out of the 11 samples synthesized C'3 (73%) and 9 synthesized SC (82%).

Carcinoma in situ

All 7 samples examined by immunofluorescence displayed numerous plasmacytes around the cervical glands and under the surface epithelium. The carcinoma

in situ was present in four different samples examined by immunofluorescence. There was no difference in the extent of the plasmacytic infiltration between the samples with carcinoma-in-situ and the samples at distance from the carcinoma. In all the cases the IgG plasmacytes were more numerous than IgA plasmacytes (Fig. 3A and B). In two samples there were rare cells positive for IgM. Six samples were cultured in vitro, they all synthesized both IgG and IgA. The synthesis was marked.

Epidermoid Carcinoma

Of the 16 samples examined by immunofluorescence, 15 showed numerous plasmacytes (Fig. 3C and D). These plasmacytes were present in the stroma of the tumor, they were irregularly distributed and were often displayed as small colonies. There were very few plasmacytes in the neoplastic cords. Immunoglobulins were never seen on the surface nor in the cytoplasm of tumor cells.

All 15 samples cultured in vitro synthesized immunoglobulins, the IgG synthesis was marked and always predominant (Fig. 2C).

Endometrium in Proliferative Phase

Twenty samples were examined by immunofluorescence and none of them showed plasmacytes. The chorion was always imbibed by IgG. The glandular epithelium was never positive for IgA nor for IgG.

Twenty two samples were cultured in vitro. Two of them synthesized trace amounts of IgG (Table 2).

Endometrium in Inactive Phase

Four out of five samples examined by immunofluorescence showed a pattern similar to that of endometrium in the proliferative phase. The fifth sample showed numerous IgG plasmacytes infiltrating the chorion in small foci. Histologic examination of other areas of the same sample showed tuberculous granulomata.

Six samples were cultured in vitro. The sample from endometrium with tuberculosis synthesized large amounts of IgG as assessed by the intensity of the labeled line.

Endometrium in Secretory Phase

Sixteen samples were examined by immunofluorescence. The chorion in all the samples was imbibed by IgG. In 4 samples there were very occasional plasmacytes in the chorion. The epithelial cells did not contain any immunoglobulins.

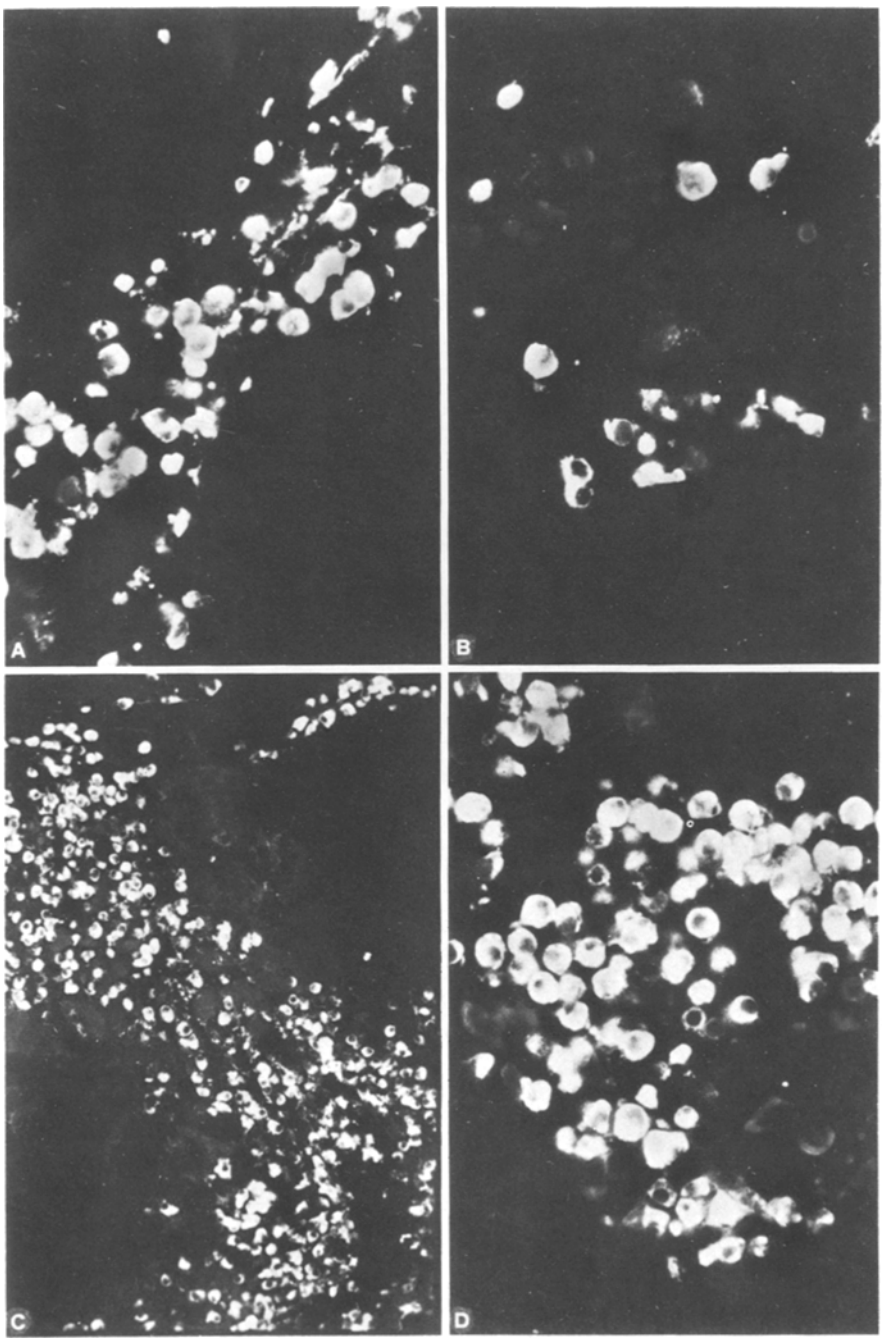

Fig. 3A–D. Immunofluorescence of various cervical tissues with antisera specific for IgG and IgA. **A** Carcinoma in situ with antiserum specific for IgG. Numerous plasmacytes are present beneath the epithelium. ×560. **B** Same carcinoma with antiserum specific for IgA. ×560. **C** Epidermoid carcinoma with antiserum specific for IgG. Numerous IgG plasmacytes are seen in the stroma of the tumor. ×220. **D** Same tumor with antiserum specific for IgG. ×560

Table 2. Synthesis of C'3, IgG, IgA and secretory component by endometrium. Results given for IgG and IgA are the summation of in vitro synthesis and immunofluorescence. Results given for C'3 and secretory component are those of in vitro synthesis only

	Immunoglobulins			C'3	Secretory component		
	G	A	O		free SC	free SC + SIgA	SIgA
Proliferative phase (22)	2	1	19	18	2	0	0
Secretory phase (17)	0	4	13	14	11	2	0
Inactive phase (6)	3	1	2	5	1	1	0
Carcinoma (4)	3	0	1	2	2	0	0

G = predominance of IgG; A = predominance of IgA;
O = absence of immunoglobulins; Numbers of cases are given in parentheses

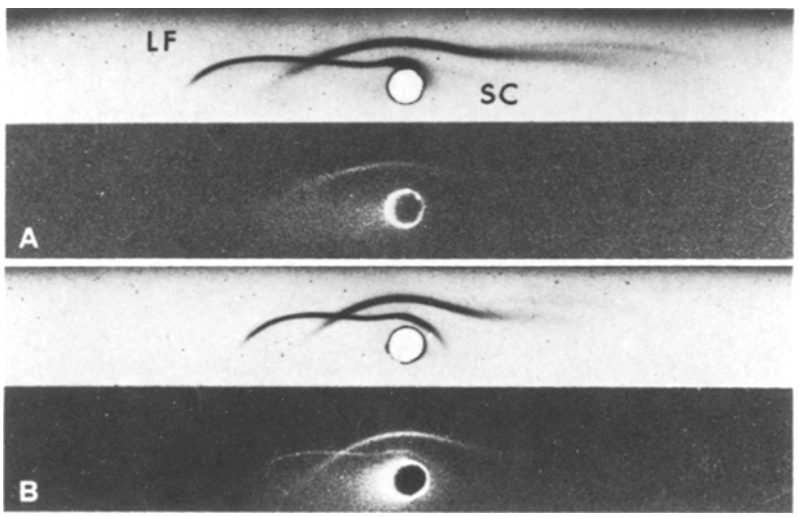

Fig. 4A and B. Autoradiographs of immunoelectrophoresis with human milk as carrier and antiserum specific for free secretory component. The corresponding stained slide is shown on top of each autoradiograph. **A** Culture fluid from adenocarcinoma of the endometrium. Labeling of the free secretory component (*SC*). **B** Culture fluid from endometrium in the secretory phase. Labeling of lactoferrin (*LF*) and free secretory component (*SC*)

Out of 17 samples cultured in vitro, 4 synthesized immunoglobulins; three of these were examined by immunofluorescence and contained plasmacytes. In all cases the synthesis was low. Thirteen samples synthesized SC (77%) (Fig. 4B); in 11 cases secretory component was synthesized alone, and in two cases only was it synthesized in an unbound state and bound to IgA.

Carcinoma

Four carcinomas were examined by immunofluorescence. In 3 samples there were numerous IgG and IgA plasmacytes with a predominance of the IgG type, and in 1 sample, only IgG plasmacytes were seen. The cytoplasm of tumor cells did not contain any immunoglobulins. Four samples were cultured in vitro and synthesis of immunoglobulins and free secretory component (Fig. 4A) was demonstrated in 2 samples only.

Discussion

The majority of the cervical tissues which were examined synthesized immunoglobulins. By immunofluorescence the plasmacytes were seen to be irregularly distributed in the tissues and the results obtained on a random sample are perhaps not representative of the entire mucosa of the cervix. However, the results of the in vitro cultures made with other samples are in agreement with those from immunofluorescence, and in most cases there is a good correlation between the number of plasmacytes positive for a given immunoglobulin class and the in vitro synthesis of this immunoglobulin. Therefore, by taking into account the results from the two methods, we have a valid estimate of the production of immunoglobulins.

Cervical tissues without lesions synthesized only trace amounts of immunoglobulins and the number of plasmacytes infiltrating the mucosa was low. Similar observations have been reported by several authors on few samples (Lippes et al., 1970; Rebello et al., 1975) and by Hutcheson et al. (1974) on a larger series. Moreover, only 26% of the cervical tissues had a predominant IgA synthesis. These observations differ from those made in other mucosal membranes like the respiratory or the gastro-intestinal mucosae (Tourville et al., 1969; Brandtzaeg and Baklien, 1976). The fact that in 9 samples only free secretory component was synthesized and that in 12 cases free and bound secretory component were synthesized, also demonstrates that secretory component is synthesized in excess when compared with the synthesis of IgA. In contradiction to these results, Rebello et al. (1975) not only observed numerous plasmacytes in the cervical tissues they examined, but also a constant predominance of IgA plasmacytes. An explanation for this contradiction probably lies in the difference between the age groups of the patients whose cervical tissues were studied; those of Rebello et al. (1975) had a mean age of 41 years and ours a mean age of 49 years. When the group of 27 cervical tissues in our study is subdivided into two age groups, predominance of IgA synthesis is observed in 5 out of 9 samples from patients in the age group between 39 to 43 years and in only 2 out 18 samples from patients in the age group between 44 and 68 years. It seems therefore that some characteristics of the secretory immunological system are blurred with age, and that IgA plasmacytes are replaced by IgG cells. Our observations are in agreement with those of Waldman et al. (1971) who have reported that with increasing age, there is an increase of IgG and a decrease of IgA in vaginal secretions.

Neither local modifications of the cervical epithelium nor inflammation seem to stimulate the local secretory immunological system, since there is almost exclusively IgG synthesis. This is not what Chipperfield and Evans (1972) have reported since they describe a predominance of IgA cells consequent to cervical inflammation. However, this discrepancy is probably more apparent than real. Our tissue samples were washed for 12 h in phosphate buffered saline. This reduces or suppresses the diffuse IgG fluorescence in the stroma and allows a better detection of IgG cells (Brandtzaeg, 1974b). Chipperfield and Evans (1972) also used materials from patients between 18 and 30 years of age, whereas the age of our patients varied between 26 and 50 years. Finally, several cases reported by these authors have as many IgG plasmacytes as IgA cells in the cervical tissues.

Thus, although the cervix has a secretory immunological system, it is also capable of mounting an immunological response with a predominance of antibodies different from secretory IgA. This would explain the presence of IgG in some vaginal secretions, which have not necessarily originated from the serum by transudation (Chodirker and Tomasi, 1963; Masson et al., 1969), and also the appearance of antibodies of IgM class following local immunization (Waldman et al., 1972). The factors which make the local secretory immunological system more or less responsive are certainly numerous but increase in age probably represses this system.

Local synthesis of IgG was particularly strong in epidermoid carcinomas and numerous plasmacytes infiltrated the stroma of these tumors. It could be that these cells synthesized antibodies against specific tumor antigens; antibodies against cervical cancer cells have been detected in the sera of cervical cancer patients (Chiang et al., 1976). The role of these locally synthesized antibodies on the evolution of the tumor remains to be determined. It could also be that the appearance of local plasmacytes is part of the inflammatory reaction to infection of the tumor and/or necrosis. Whatever the explanation may be, the carcinoma apparently has no effects on the local secretory immunological system. However, stimulation of this system by carcinoma has been described for carcinomas in several mucosal membranes; the secretory response is expressed by an increase of SIgA in the secretions or in the serum (Levy et al., 1975; Logerfo and McLanahan, 1975; Weisz-Carrington et al., 1976) and also an increase of serum type IgA in the serum (Dent and Bienenstock, 1974).

The synthesis of secretory component is almost the same in normal cervical tissues, tissues with inflammation, carcinoma in situ and metaplasia; between 82% and 89% of the tissues synthesize secretory component. However, only 12% of the epidermoid carcinomas synthesized this component. The tumor cells (Logerfo and McLanahan, 1976) either derive from cells which are unable to synthesize SC or have lost their ability to synthesize SC, this has also been observed in some carcinomas of the colon (Poger et al., 1976).

It has been suggested that SC plays a role in the transepithelial transport of IgA as well as in the homing of IgA commited lymphocytes in mucosal membranes (Strober et al., 1976; Weisz-Carrington et al., 1976). Our results on cervical tissues do not seem to support this last hypothesis. Nine out of the 27 cervical tissues without lesions synthesized SC and there were no IgA plasmacytes in the tissues, and no local synthesis of IgA.

Cervical tissues with carcinoma give similar results; the 2 carcinomatous tissues which synthesized SC did not synthesize IgA and did not have IgA plasmacytes in their stroma. This absence of correlation between the synthesis of SC and the number of plasmacytes has also been described for the epithelium of the gall-bladder which synthesized SC but which is not infiltrated by IgA plasmacytes in the absence of inflammation (Poger and Lamm, 1974).

There was no difference in C'3 synthesis between the various cervical tissues except in the cases of carcinoma in situ and the epidermoid carcinomas, where C'3 was less frequently detected. C'3 is probably synthesized by macrophages, as in many other tissues (Stecker and Thorbecke, 1967); its local significance is uncertain.

With one exception, the endometrial tissues examined did not synthesize immunoglobulins and were not infiltrated with plasmacytes. The only case in which IgG and IgA plasmacytes were observed and in which IgG and serum type IgA synthesis was detected, was an endometrium with tuberculosis.

The secretory component is synthesized mainly by endometrium in the secretory phase; this confirms the observations made by immunofluorescence in which the glandular epithelium of the endometrial tissue was positive for SC essentially in the secretory phase (Tourville et al., 1970). The hormonal dependancy of synthesis of SC might explain the synthesis of this protein by two endometrial tissues in the inactive phase; these tissues were taken from patients under progestogen therapy. As with the cervix, endometrial synthesis of secretory component is not concomitant with IgA plasmacyte infiltration and synthesis of IgA; out of the 13 endometrial tissues synthesizing SC, only 2 showed IgA plasmacytes and two endometrial tissues which did not synthesize SC were infiltrated with plasmacytes. Two out of 4 carcinomas of endometrium synthesized secretory component. Whether the adenocarcinomas which can synthesize SC are better differentiated than the carcinomas which cannot synthesize this protein, and whether there is a relationship between the SC synthesis and the prognosis of the tumor is open to study. Here again, SC synthesis was not accompanied by an IgA plasmacyte infiltration of the tumor.

As in cervical tissues, C'3 was uniformly synthesized in almost all the endometrial tissues except in the carcinomas of which only 2 of 4 synthesized C'3.

Cervical tissues and endometrium are fully adapted for a secretory immunological response. However, local changes such as carcinoma or infection stimulate the formation of antibodies of IgG class. This suggests that stimulation of the secretory immunological system is only realized under very special conditions. Moreover, it seems unlikely that SC plays an important role in the localization of cells committed to IgA synthesis. Whether a relationship exists between the weakening of the local secretory immunological system and the incidence of carcinoma remains to be established.

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