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Letter to the Editors

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Dear Sirs,

We wish to comment on some concepts and methodological aspects of the recent article in *Virchows Archiv A* entitled "Altered expression of Lewis blood group and related antigens in fetal, normal adult and malignant tissues of the uterine endometrium" by Inoue et al. (1990). In this article, the authors examine the expression of Lewis system antigens in the endometrium of normal adults and fetus and their alterations in the carcinoma.

The authors specifically mention the "oncofetal" characteristic of Lewis a and Lewis b antigens and of the "carcinoembryonic characteristic" of Lewis b antigen. The antigens of the Lewis (Lewis a, Lewis b) system, based on type 1 chain, are structures abundantly present in the normal epithelium of adults and, in general, their presence in these tissues depends on glycosyltransferases coded by Lewis and secretor genes (Oriol 1986, 1987). In mucosecretory epithelium, individuals who carry both genes, synthesize Lewis b; in the absence of the secretory gene, this last antigene cannot be synthesized and the entire precursor of chain type 1 is transformed into Lewis a. Individuals who do not carry the Lewis gene do not express either Lewis a or Lewis b in these epithelium (Watkins 1980). Therefore, it is absolutely necessary to correlate the phenotype Lewis of individuals and, if possible, their secretor status with the expression of these antigenes both in normal and pathologic tissues in order to obtain a correct interpretation of the alterations that are produced in this antigenic system. If this is not done as so and only the global presence is observed of any antigen in a given number of individuals, erroneous conclusions can easily be established.

As the authors state, various antigenic alterations of this system in different neoplasias have been described (Blasco 1989; Lloyd 1987; Sakamoto 1989; Torrado 1989). These fundamentally consist in the loss of the Lewis isoantigenes caused by incomplete synthesis with or without precursor accumulation and aberrant glycosylation with neosynthesis of antigens (Hakomori 1985, 1988; Lloyd 1987). To evaluate each phenomenon, specially the first (e.g. anomalous expression of Lewis a antigen in Lewis (a−b+) phenotype individuals), it is necessary to correlate the phenotype of the patient with the expression of Lewis antigens in the lesion. In the materials and methods section, the authors state that the patient's blood type was determined; although, in the rest of the article they do not correlate these data with the results.

We believe that there are methodological errors in this article which may possibly affect the authors' conclusions.

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Reply

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Dear Sirs,

I would like to thank Dr. Torrado and his collaborators for their comments on our recent article "Altered Expression of Lewis Blood Group and Related Antigens

in fetal, normal adult, and malignant tissues of the uterine endometrium".

As has been pointed out, it is well known that the Lewis phenotype of red blood cell (RBC) is controlled by interaction between secretor and Lewis genes. There is also speculation that carbohydrate determinants of Lewis antigens found on RBC are not produced in the RBC itself, but rather are produced in the muco-epithelium of alimentary tract, enter into circulation and then attach to RBCs. However, this concept has not been verified. In addition, the glandular cells of uterine endometrium are not mucosecretory epithelial cells and have not been investigated from the point of the expression of Lewis antigens. Therefore, even if the secretory status and phenotype of Lewis antigen were not determined in individuals, this does not deny the value of our results for the following reasons.

(1) In our study, 16 out of 63 normal adult tissues (25%) were negative for both Lewis-a and -b, while the same phenotype (Le^a_- Le^b_-) was observed in 6 (8%) out of 73 cancer tissues. Four of these 6 cases were poorly differentiated adenocarcinomas. Of the 51 well-differentiated adenocarcinomas, only one (2%) showed Le^a_- Le^b_-. This difference could not have been produced by chance as both groups contained a large number of cases. Thus, an increased expression of Le^a and Le^b in endometrial cancers can be proposed. This speculation is further supported by the finding that Lewis antigens are expressed in cancer tissues but absent in the adjacent normal glands.

(2) Sakamoto et al. (1989) reported the expression of both antigens (Le^a and Le^b) in 12 of 31 normal gastric epithelia. We also observed the same phenomenon in 15 of 63 normal endometria. However this phenotype (Le^a_+ Le^b_+) is not present on RBC. Urothelia obtained from 4 individuals with Le^a_- Le^b_- revealed either Le^a or Le^b expression in two of them. All 32 uterine endocervical glandular tissues (data not shown) showed expression of Le^a or Le^b. Similarly, none of the 14 cases showed Le^a_- Le^b_- phenotype in normal and benign pancreatic tissue, while individuals with this phenotype represent 10% of the population by RBC phenotyping. These results indicate that Lewis phenotype of RBC is different from that of the tissues. Similarly, "secretor" and "non-secretor" indicate the capacity of an individual to secrete or not secrete blood group substances in saliva. This status is not always consistent with that of tissues. Comparison of Lewis phenotyping between saliva and RBC have also shown some discrepancies in one study (Ichihara et al., personal communication). The expression of these antigens on gastrointestinal tissues is different from their phenotypes determined by RBC or saliva. In fact, of 9 non-secretor individuals (Le^a_+ Le^b_-), 2 showed Le^a_+ Le^b_+ and another 2 showed Le^a_- Le^b_- in normal gastric epithelium. Thus, the expression of blood group antigens on tissues does not always depend on the phenotype of RBC and secretor or non-secretor status in saliva.

(3) Uterine endometrial glands are not mucosecretory epithela. Therefore, they might be less affected than alimentary epithelium by "secretor" or "non-secretor" status of persons.

We understand that the Lewis/secretor status of normal adults and cancer patients should have been included in order to make our study more meaningful. We are planning to do so in our next study. However, as we mentioned in the second paragraph of this letter, the phenotype of each individual determined by either RBC or saliva does not always give definitive information about genetic background of the person. Studies at the genetic and molecular level are needed for complete understanding of the influence of secretor status on blood group antigen expression. At the present time, we believe that our study provides several important points about altered expression of blood group antigens associated with carcinogenesis.

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