spindle shape and osteoclast-like giant cells and prominent vascularity in the excised tumor by histopathologic examination and diffuse osteoporosis by x-rays. Disappearance of hypophosphatemia, hyperphosphaturia, glycosuria, proteinuria and the dramatic clearance of his symptoms following removal of the tumor were also con-firmatory evidences for the diagnosis of oncogenous osteomalacia. Recognition and removal of the tumor in patients with oncogenous osteomalacia restores the severe and total disability (7). In conclusion, oncogenous osteomalacia should be suspected in any patient who presents with metabolic bone disease associated with hypophosphatemia and inappropriate phosphaturia, in combination with a benign mesenchymal soft tissue or bone tumor. The possibility of metastatic malignant disease should be ruled out by biopsies of the bones guided by bone scan or x-ray examinations.

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IS GASTRIC CANCER HETEROGENEITY THE CLUE TO HLA-DR ASSOCIATED SUSCEPTIBILITY?

Worldwide, gastric cancer remains a leading cause of cancer death (1). Despite recent advances (2), the role of genetic and immune factors for the development of gastric cancer remains unclear. A genetic component was suggested when increased frequency of blood group A was found in patients with gastric cancer (3). Subsequent studies have confirmed that heredity may be important for the development of this malignancy (4–7). The genetic regulation of immune phenomena mainly occurs within MHC, and HLA-DR antigens play a crucial part in initiating the specific immune response. It has therefore been suggested that phenotypic HLA-DR differences may be associated with different risks of developing neoplastic diseases. However, in three reported population studies on HLA-DR and gastric cancer no constant relation was found (8–10), and the same concerned earlier investigations of HLA class I antigens (11–13). One reason for the conflicting results may be gastric cancer heterogeneity (1, 2, 14, 15). These facts prompted us to investigate the association of HLA-DR antigens with gastric cancer taking into consideration its types according to the Järvi-Lauren classification, tumour grade, stage, and topographical classification.

Material and Methods. Forty-six consecutive, unrelated patients (35 males and 11 females) of Polish ancestry with resectable and histologically proven gastric carcinoma have been prospectively tested since 1989 and typed for 10 HLA-DR specificies (DR1, DR2, DR3, DR4, DR5, DRw6, DR7, DRw8, DR9, DRw10) by a standard microlymphocytotoxicity technique (16, 17). Lymphocytes were isolated by gradient centrifugation and T and B cell separation was performed with AET-treated sheep erythrocytes. The serotyping trays were 'Lymphotype-DR' (Biotest Diagnostics). The controls consisted of 389 Polish individuals. Antigen frequencies were calculated in the control group, the total cancer group and in subgroups of patients categorized according to the Järvi-Lauren classification (14) (24 patients with intestinal type (Int), 14 with diffuse type (Dif) and 32 with intestinal and mixed types (Int + M)), WHO histological grading (15) (26 patients with adenocarcinomas with high or moderate grade of differentiation (H + M) and 20 with poorly differentiated adenocarcinoma or undifferentiated carcinoma (P + U)), TNM-AJC classification of tumour extension—T (15) (12 patients with T1 or T2, 43 with T2 or T3 or T4, 22 with T1 or T2 or T3, and 24 with T4) and topographical classification (15 patients with the tumour located in the cardiac region—Car, 27 in the fundus or body—Fun + Cor, 21 in the pyloric region—Pyl). The antigen frequencies in the groups were compared using the χ^2 test with Yates' correction. The strength of association was estimated by calculating the relative risk (RR).

Results. HLA-DR typing results in the 46 patients with gastric cancer are shown in Table 1. Only the HLA-DR5 frequency was

Table 1

HLA-DR antigens distribution among 46 gastric cancer patients and 389 controls

HLA specificity	Frequency (%) patients	Frequency (%) controls	χ^2	p-value
DR1	28.3	20.3	1.12	N.S.
DR2	23.9	25.2	<0.01	N.S.
DR3	19.6	22.4	0.06	N.S.
DR4	17.4	19.3	0.01	N.S.
DR5*	34.8	20.1	4.44	< 0.05
DRw6	13.0	14.9	0.01	N.S.
DR7	21.7	26.5	0.27	N.S.
DRw8	4.3	5.7	<0.01	N.S.
DR9	4.3	3.6	0.03	N.S.
DRw10	4.3	3.3	<0.01	N.S.
DRx	28.3	38.6	1.45	N.S.

* RR = 2.13
DRx—unidentified antigens or homozygotes

Table 2

Prevalence of HLA-DR5 in subgroups of gastric cancer patients according to location, stage, histological grading and Järvi-Lauren classification when compared to 389 controls (20.1%)

Subgroup of patients	n	HLA-DR5 frequency (%)	χ^2	p-value
Car	15	40	2.38	N.S.
Fun + Cor	27	25	0.24	N.S.
Pyl	21	38	2.90	N.S.
T1 + T2	12	33	0.58	N.S.
T2 + T3 + T4	43	30	1.84	N.S.
T1 + T2 + T3	22	32	1.11	N.S.
T4	24	38	3.16	N.S.
H + M	26	31	1.11	N.S.
P + U	20	35	1.75	N.S.
Int	24	25	0.10	N.S.
Int + M	32	28	0.74	N.S.
Dif*	14	50	5.59	< 0.02

* RR = 3.99
Abbreviations—see Material and Methods

found to be significantly increased (34.8% vs. 20.1% in controls; $p < 0.05$; RR = 2.13). As in the combined group the antigen frequencies for none of the remaining specificities were significantly different from controls in the subgroups categorized according to gastric cancer heterogeneity. More attention should be paid to Table 2, where HLA-DR5 frequencies in the subgroups are specified. Only for the diffuse type gastric cancer the HLA-DR5 frequency was significantly elevated (50% vs. 20.1% in controls; $p < 0.02$; RR = 3.99). No significant HLA-DR5 frequency deviations from controls were noted in the other groups.

Discussion. Traditional population studies of HLA class I antigen association with gastric cancer have not yielded any striking conclusions (11–13). The same is true for the very few investigations on incidence of HLA class II antigens in patients with this malignancy. Kitsuta et al. (8) were the first to report a significant increase in the frequency of HLA-DR5 (RR = 3.5) amongst Japanese patients with gastric cancer. They found the antigen to be especially associated with the advanced, undifferentiated, Borrmann's type 4 tumours. Subsequent studies have not taken the disease heterogeneity into account and the pioneer work of Kitsuta's group was not quoted. Martell et al. (9) could not demonstrate any HLA-DR association with gastric cancer in coloured patients in the Cape province. However, in patients from Andrapradesh, the neoplasm was reported by Jayanthi et al. (10) to be positively associated with HLA-DR3 (RR = 3.22). As far as we know, our study is the first in which DR loci have been examined in European Caucasian patients. Our results are partially compatible with those obtained by Kitsuta et al. (8) and demonstrate that the HLA antigen DR5 frequency is significantly increased in patients with gastric cancer, particularly among those with the diffuse type according to the Järvi-Lauren classification. This classification recognizes 2 main subtypes of gastric cancer (intestinal and diffuse) as having independent biological characteristics (1, 2, 14). Nomura et al. (13) suggested a study on possible association between HLA-DR and the subtypes but this proposal has not previously been realized. Our results indicate that HLA-DR5 may be associated with the diffuse type. This is in a way supported by the study of Kitsuta et al. (8) as the advanced, undifferentiated type and Borrmann's type 4 are common among diffuse gastric cancers (7, 14). In our study HLA-DR5 frequencies were insignificantly increased in the corresponding subgroups.

It is well known that disease heterogeneity may mask a potential association with a specific risk factor (18). Possible primary HLA-DR5 association with the diffuse type of gastric cancer might have been responsible for the lack of consistency in previous reports. It is plausible that the examined groups were dominated by the intestinal and mixed type patients. A specific role of genetic factors for the susceptibility to diffuse gastric cancer has been proposed by Correa et al. (7).

Our results are preliminary and require more sophisticated confirmation. We are also aware of the danger of statistical bias when multiple comparisons are performed. However, it seems possible that the gastric cancer heterogeneity based on the Järvi-Lauren classification can be the clue to HLA-DR associated susceptibility.

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THE ROLE OF RADIOTHERAPY IN TYMPANOJUGULAR CHEMODECTOMAS

Chemodectomas are uncommon non-chromaffin paragangliomas (1, 2). They are histologically benign, consisting of epithelioid cells within stroma and blood vessels and non-myelinated nerve fibers and may originate anywhere glomus bodies are found, e.g. often near the bifurcation of the common carotid artery and in the temporal bone. Depending on the location, chemodectomas can be classified as tympanic, jugular, carotic or according to other specified locations (3). A chemodectoma originating from glomus tympanicum is located in the middle ear. It may invade the mastoid bone, the external auditory canal, the semicircular canal and the facial nerve canal. Glomus jugular chemodectoma may involve the base of skull, the jugular vein, the cranial fossae and the middle ear (3). Metastases occur in less than 5% of all chemodectomas (4). Several case reports have appeared in the literature. However, the rarity of chemodectoma makes it difficult to establish guidelines for treatment, and no single institution has significant experience. The purpose of this article is to present the experience of seven patients treated at Helsinki University Central Hospital during 1967–1990, as well as a summary of the literature.

Radiation therapy. All patients, except one (case 1) were given external radiotherapy, three (cases 3, 5, 7) with ^{60}Co beam and three (cases 2, 4, 6) with 6 MV x-rays. The total dose varied from 40 to 60 Gy given with 2 Gy per fraction 5 days/week over a time between 31 and 60 days. Two patients (cases 3, 5) had a planned 3 weeks' rest in the middle of the treatment (split-course), whereas one patient (case 6) had two weeks' interruption due to mucosal reactions. An individual treatment plan with two fields was used in all cases with field sizes ranging from 24 to 72 cm^2. The planning was adjusted to achieve an adequate dose in the primary tumour with a 1–2 cm margin. The tumour was considered to be controlled if there was no progression of cranial nerve defects or other specific symptoms and no increase in size of visible or radiographic tumour. The follow-up time was counted from the end of the radiotherapy.

Case 1. A 55-year-old man presented with pain and hearing loss in left ear. After radical operation he received postoperative radiotherapy in November 1961 by application of ^{60}Co beans in the tympanic cavity achieving a total dose of 53 Gy in 12 days. He remained symptom-free for 13 years until death of myocardial infarction in July 1974.

Case 2. A 37-year-old woman had suffered from persisting tinnitus in her left ear for a couple of years. Nine years after a radical operation an inoperable recurrence was diagnosed invading jugular fossa and surrounding bone. She received a total dose of 50 Gy in 35 days in September 1991. She is alive and well after 2 years' follow-up, and was last seen in April 1993.

Case 3. A 67-year-old woman had a sense of loud sound in her left ear. In March 1988, nine years after radical operation, she received 50 Gy radiotherapy in an inoperable local recurrence, during which she had severe vertigo. She lived another four years until she died in May 1992 with tumour progression into the brain.

Case 4. A 62-year-old woman experienced hearing loss and pain in her right ear. In July 1979, 14 years after radical operation she received radiotherapy for a large recurrence which, however was stopped already at 40 Gy due to severe vertigo. She died in August 1983 with tumour progression into the brain through the base of the skull.

Case 5. A 67-year-old man lost his hearing on the right ear and was first treated for a right-sided tympanojugular tumour by a non-radical resection. He received postoperative radiotherapy up to a total dose of 60 Gy in October 1986. This patient is still alive and well after 6 years' follow-up and was last seen in March 1992.

Case 6. A 54-year-old woman presented with hearing loss. The tumour which involved with left tympanic cavity and jugular fossa, was considered inoperable and was treated by radiotherapy (54 Gy) in August 1985. She has been followed for 7 years, and is still alive without any sign of recurrence. She was last seen in December 1992.

Case 7. A 67-year-old woman noted tinnitus in her left ear. She received 50 Gy for an inoperable tympanic chemodectoma in December 1988. During the radiotherapy she experienced severe vertigo, but this did not change the planned radiotherapy. This patient is alive and well after 4 years from the radiotherapy and was last seen in June 1993.

Discussion. Despite their benign nature, chemodectomas can cause severe symptoms when invading vital regions, e.g. the brain via the base of the skull. Symptoms are generally present for up to a couple of years before diagnosis, as the tumours grow slowly. Local excision is the treatment of choice for small resectable tympanic tumours (5), but when the jugular bulb is involved or the tumour invades the bone, the local tumour control rate for surgery alone is only 50–60% (6). Some surgeons advocate operative procedures even for extensive lesions despite the high risk of complications (7). Since these tumours are generally extremely vascular, radical surgery may be difficult and hazardous, and postoperative radiation is frequently recommended (4, 6).

When the glomus tumour is located near the jugular foramen, the lesion is not often radically operable, but can be treated effectively by radiation therapy. Local control of the tumour can be improved by postoperative radiation therapy (6, 8). Good results have also been achieved by radiotherapy alone for unresectable tumours (6, 9, 10).

Radiation therapy has been given with various schedules: 35 Gy in three weeks (11), 40–50 Gy in 4 to 5 weeks (8), 45–50 Gy in 5 weeks (12), and 50–60 Gy in 5 to 6 weeks (12). Equally good outcome has been reported from each of these schedules (8, 11, 12). Chemodectomas seem to regress slowly after radiotherapy reflecting late response to radiation (6). This has been observed