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Cancer Cells in the Circulating Blood of Patients with Larynx Cancer. Part I

Krążące komórki nowotworowe we krwi żylnej chorych z rakiem krtani. Cz. I

Свободно циркулирующие клетки злокачественной опухоли в венозной крови больных раком гортани. Ч. I

Studies on the occurrence of free cancer cells in the venous blood of patients with carcinoma do not belong to those which attract the investigators' attention, because of the particularly difficult and time consuming methods: concentration of cells, staining, diagnostic evaluation, coloured photographical documentation. Furthermore, the interpretation of the results of the studies is connected with considerable difficulties in the selection of respectively large clinical material concerning such an oncological unit which would involve morphological and clinical conditions enabling various disseminations of cancer cells into the system of lymphatic and venous vessels as well as the possibility of these studies with the actual local condition of the tumor. The intrinsic cancer of the larynx belongs to such a disease.

The purpose of the studies was:

1. To determine whether in patients with larynx cancer, or after its treatment, free tumous cells can be found in peripheral venous blood and in the blood draining from the tumour.
2. To learn the existing correlations between the clinical conditions of the patients with cancer of the larynx and the occurrence of free tumor cells in venous blood, if such cells are found.
3. To ascertain whether the occurrence of f.t.c. in venous blood of patients with larynx cancer before primary therapy made their radical treatment according to the oncological criteria used at present impossible.
4. To ascertain whether the occurrence of f.t.c. in venous blood of patients treated for larynx cancer, or after their treatment, was of some prognostic value for the survival of the patients.
5. To study the influence of operative trauma (total laryngectomy) on the distribution of f.t.c. in the venous blood.

The studies were carried out on a group of 108 patients treated and controlled after the treatment for larynx cancer at the Otolaryngological Clinic in Lublin in the years 1967—1971. The average age of the patients was 56 years; this group consisted of 4 women and 104 men. The clinical diagnosis of the patients was confirmed by histological examination. The patients were divided into several groups with regard to the localization of the cancer, its

advancement and histological malignancy. Tumour cells in the venous blood were searched for in various periods of the studies. Some of these patients were attached to two or more clinical groups; however, each of them belonged only once to a definite group studied. Group A — 78 persons in whom free tumour cells were searched for in the peripheral venous blood before and after primary treatment of the cancer. Group B — 45 persons in whom free tumour cells were searched for in the peripheral venous blood before and after (5—7 days) radical surgical treatment — total laryngectomy most frequently with the thorough extirpation of the regional system of cervical lymphatic vessels and nodes by the method of Jawdyńsky-Crile, and in the blood draining from the tumour during the operation. Group C — 40 persons in whom f.t.c. were searched for in the peripheral venous blood during the period of 1 to 5 years after the total extirpation of the larynx together with the cervical lymphatic system.

Patients who were being treated with irradiation or had just finished it, those treated with blood transfusion, and those who were after severe infections diseases, or after hemorrhages were excluded from the studies on free cancer cells. One patient with supraglottic carcinoma as well as cases of total laryngectomy, which during the operation appeared technically non-radical with regard to the primary focus, were not taken into consideration either. The post-operative evaluation of feature N was omitted because it was not histologically controlled in all patients operated. Such a selection of the patients treated and persons after treatment for laryngeal cancer in groups B and C was indispensable to obtain comparative material in relation to the occurrence of f.t.c. in the examination periods. This selection was also possible because comparative evaluation of the results of treatment was not the purpose of the author's studies.

In the evaluation of clinical advancement of carcinoma of the larynx the author used the modification of the international classification of larynx cancer of the type TNM developed by the American Joint Committee for Cancer Staging and End Results Reporting — AJC (1), as more convenient for clinical selection of patients in these studies. In the tables only these combinations of TNM features were given, which were attributed to the studies patients. In histological selection the classification of W a h i *et al.* was used (20). For the isolation and concentration of f.t.c. in venous blood the method of M a l m g r e n *et al.* (12) in its modification given by L o n g *et al.* (11) was used. The preparations were examined by using the cytofluorescence technique described by B e r t a l a n f f y (2, 3, 4, 5) — staining with acridine orange (AO). To test the methods used for the concentration and isolation of free tumour cells from the blood, their staining and inspecting as well as the diagnostic evaluation and photographing, the author carried out model studies (control of the staining model), experimental studies (control of concentration efficiency) and control studies (control of diagnostic evaluation) — (10). The preparations were inspected in the fluorescence microscope Zeiss (HBO — 200). Coloured documentation of the studies was accomplished by using ORWO chrome films — colour reversal UT 18. Moreover those preparations stained by the AO method of B e r t a l a n f f y, in which cancer cells or suspected ones were found, were decolourized and fixed and stained again by means of hematoxylin and eosin according to the commonly used methods. Thus only those results were considered as positive which were confirmed by using the

method of classical staining. Divergency in the evaluation of the results were considered as positive which were confirmed by using the method of classical staining. Divergency in the evaluation of the results of the studies obtained by using both methods (using H+E as control) did not exceed 1,5% of the determinations.

The obtained results of the search for free cancer cells in venous blood were determined by modified classification of P a p a n i c o l a o u (15):

— : lack of cancer cells, atypical or doubtful cells with regard to malignancy,

+ : malignant cancer cells, a few — up to 5 in a sample,

++ : malignant cancer cells of which 5—10 or more were found in a sample.

Negative results of the examinations were denoted by "—", positive results — by "+" and "++ , determined together for all smears of the given sample. The numerical results of the clinical and laboratory studies carried out were statistically analysed.

RESULTS

After staining the cytological preparations with acridine orange (AO), the cytoplasm of the cell fluoresced, according to the content of ribonucleic acid — from dark green through brown, orange to a red colour, whereas nuclei (containing deoxyribonucleic acid) fluoresced green, yellow and yellow-white. The cancer cells after staining showed a lively-red, glaring fluorescence of the cytoplasm, and green-yellow or yellow fluorescence of hyperchromatic nuclei. This staining readily and quickly manifested even individually appearing cancer cells in the given preparation, whose intensive red or red-orange staining practically exluded their being missed as early as on the initial inspection of the preparation under a small microscopic magnification. In further differentiation of suspected cells based on histochemical and morphological features great magnifications were used.

In the preparations of condensed blood, free tumor cells were distinctly larger than normal blood cells were distinctly larger than normal blood cells. Inspected under great magnification, they met the morphological criteria required to distinguish a cancer cell, taking into consideration the changes which cancer cells undergo in the circulating blood. In the smears from a tumor the cancer cells stained with AO resembled histological preparations fig. 2a, 2b), whereas in the peripheral blood round cells almost exclusively were found (fig. 2c). The examination of peripheral blood of the same patient showed cancer cells of a round shape (fig. 2c).

The above mentioned changes which the primary shape of the cancer cell undergoes on passing into the circulating blood were found by other authors (7, 14, 16, 19). These changes practically make the distinction of the origin of the cancer cell impossible.

The glaring fluorescence of the tumor cells cytoplasm in the examined preparations even overshadowed the intensive fluorescence of the cell nucleus itself (fig. 3), whereby its morphological estimation was made difficult. It should whereby its morphological estimation was made difficult. It should be noticed that in the majority of the f.t.c. observed in the blood of patients with larynx cancer fluorescence of the cellular nucleus was found; although it was typical for malignant cells with this method, the fluorescence observed was less glaring than that of the nuclei in cancer cells from tissue smears

of the same patients. Also reverse proportions with regard to the fluorescence intensity of the protoplasm were often observed in both kinds of cancer cells circulating in the blood and coming from smears from the tumor of the same patient, particularly, when in the smear more mature forms dominated — spinocellular.

Normal blood cells stained typically are easily recognizeable — 17. Some diagnostic difficulties can be caused by cells which are not usually found in the blood such as immature blood corpuscles or plasmocytes or histicytes. They are called „atypical cells" by some authors — the number of these cells in peripheral blood increases in carcinoma disease (13, 16, 17). Their exact examination, particularly under a great magnification, makes the observation of a number of features in the appearance of nuclei and cytoplasm and in staining distinctly differentiating them from cancer cells possible (6, 8, 9, 13, 17). According to the interpretation assumption of the investigation results as positive and negative with regard to the presence of free cancer cells, neither the percentage nor the kind of atypical cells found was determined in the blood studied. However, in the diagnostic evaluation by the AO method the most typical features should be taken into consideration, from which the differentiation of normal blood and atypical cells should be started (6, 9, 13).

The results of the studies in the experimental group (carried out similarly as with the method described by Schreck — 18) served as a control of the f.t.c. concentration method — cancer cells in venous blood examined under the laboratory conditions available. The loss of f.t.c. in the experimental determinations performed was from 6% to 11%, on the average 9± 0,156% (x±v); a higher loss than 12% occurred in no more than 3% of the determinations. On analogical percentage in the f.t.c. concentration method used by Blichowski was 11%. Taking into consideration the tolerance of the calculation error of the hemocytometer (5—10%) and that of the pipetting technique, the percentage loss with in the limits — of ± 10% is equivalent to the total recovery of cancer cells by using this method by which — as found by many authors — isolated tumour cells retained their morphological features, ability to survive and mitotic activity. Therefore, the material analysed by this method is considered by authors as competent for comparative diagnostic, qualitative and quantitative evaluation.

Clinical group A

In this group f.t.c. in peripheral blood were searched for in 78 patients before primary treatment of the cancer. Some of the patients in this group (16 persons — 20%) could not undergo radical treatment just on a primary diagnosis of the tumor. Table 1 shows the degree of clinical advancement of TNM disease (according to AJC) compared with initial localization of the cancer and the stage of its histological malignancy, and the results of the studies of peripheral blood on the occurrence of f.t.c. in the period of primary diagnosis of the cancer — before its treatment — in comparison with the clinical condition of the patients.

Fig. 1. graphically present the results of the studies on the occurrence of f.t.c. in the peripheral blood in these patients in comparison with the stage of histological malignancy of the tumor, its initial localization and clinical advancement as well as with the feature T. Dissimination of f.t.c. into peripheral venous blood and the stage of his-

tological malignancy. This relationship was analysed jointly and separately for lesions localized in the upper and medium part.

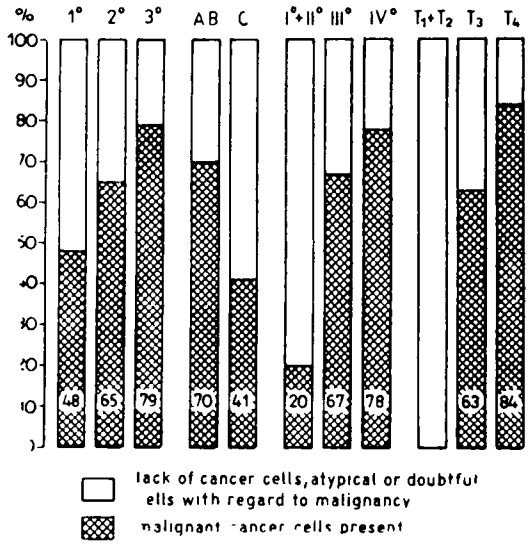

Fig. 1. Distribution of f.t.c. in peripheral blood before treatment according to the stage of histological malignancy (1°, 2°, 3°), to the site of origin (AB supraglottis — vestibulum, C glottis), to the stage of clinical advancement of the disease (I°+II°, III°, IV°) and to the tumour (T_1+T_2, T_3, T_4).

In the subgroup AR (table 1) with supraglottic localization, the presence of f.t.c. in peripheral blood was found in 11 patients (55%) from among 20 persons with stage I, in 13 patients (72,2%) out of 18 with stage II and in 15 patients (83,3%) out of 18 with stage III. Thus an increase in the distribution of f.t.c. in the blood of patients with an increase in the histological malignancy of the cancer observed; this relationship, however, was not statistically significant ($x^2=3,69$; $P<0,10$). In the subgroup C (table 1) with glottic localization, the presence of f.t.c. in peripheral blood was found in 5 patients (38,5%) out of 13 I stage persons, and in 4 patients (44,4%) out of 9 stage II and III persons treated (the stages II and III of hp. malignancy were connected in the statistical analysis because only one stage III patient was treated). This difference has an eminently random character. For both localizations (subgroup AB and C) the frequency of f.t.c. occurrence in the blood of the patients (fig. 1) was 48% in stage I (16 of the 33 treated persons), 65% in stage II (17 of the 26 treated persons), and 79% in stage III (15 of the 19 treated persons); and these differences are approximate to statistical significance ($x^2=4,99$; $P\approx0,07$). However, the analysis of the frequency of f.t.c. occurrence in all stage I patients of this group (48%), as compared with the frequency of f.t.c. occurrence together in stage II and III showed that the difference is already statistically significant ($x^2=4,12$; $r=0,23$; $P<0,05$).

Summing up the evaluation results of the correlation between the frequency of f.t.c. occurrence in peripheral blood and the stage of histological

Table 1. Distribution of f.t.c. in peripheral blood in 78 patients — group A — before treatment according to the stage of clinical advancement of the disease (TNM), to the site of origin of larynx cancer ant to its histological malignancy

Clinical advancement		Results of searching for f t c	THE SIDE OF ORIGIN OF LARYNX CANCER											
			Supraglottis (AB)				Glottis (C)				Total (ABC)			
			Stage of histological malignancy											
Stage	TNM		1°	2°	3°	Total	1°	2°	3°	Total	1°	2°	3°	Total
I°	$T_1N_0M_0$	+ +												
		+												
		−					1	1		2	1	1		2
	Total						1	1		2	1	1		2
II°	$T_2N_0M_0$	+ +												
		+												
		−	1			1	1	2	1	4	2	2	1	5
	$T_3N_0M_0$	+ +					1			1	1			1
		+		1		1						1		1
		−	2		1	3	2			2	4		1	5
	$T_4N_0M_0$	+ +												
		+	1			1					1			1
		−												
	Total		4	1	1	6	4	2	1	7	8	3	2	13
III°	$T_2N_1M_0$	+ +												
		+												
		−					1			1	1			1
	$T_3N_1M_0$	+ +		2	5	7		1		1		3	5	8
		+	2	6	4	12	2	2		4	4	8	4	16
		−	4	4		8	2	1		3	6	5		11
	Total		6	12	9	27	5	4		9	11	16	9	36
IV°	$T_4N_1M_0$	+ +			1	1		1		1		1	1	2
		+	2	1	1	4					2	1	1	4
		−	1	1	1	3					1	1	1	3
	$T_3N_2M_0$	+ +		2	1	3						2	1	3
		+	1		1	2	1			1	2		1	3
		−	1		1	2	1			1	2		1	3
	$T_4N_2M_0$	+ +	3	1	2	6					3	1	2	6
		+	2			2	1			1	3			3
		−												
	Total		10	5	8	23	3	1		4	13	6	8	27
Total (I°+II°+III°+IV°)		L	20	18	18	56	13	8	1	22	33	26	19	78
		%	26	23	23	72	17	10	1	28	42	34	24	100

malignancy of the tumor in the group studied, it can be concluded that the frequency of f.t.c. occurrence increased with the number of patients with a more malignant histological form of laryngeal cancer; the insignificance of this relationship in the subgroups AB and C analysed separately results mainly from a small number of the patients studied with these localizations of the patients studied with these localizations of the tumor.

Dissemination of f.t.c. in peripheral venous blood. and initial localization of cancer. The occurrence of f.t.c. was found in 39 patients (70%) of the 56 treated persons with supraglottic localization (AB), and in 9 patients (41%) of the 22 treated persons with glottic localization (C) of the tumor; these differences are already statistically significant ($x^2=5{,}51$; $r=0{,}27$; $P<0{,}02$). Supraglottic localization of larynx cancer

in the group studied affected a more frequent dissemination of its cells into venous blood.

Dissemination of f.t.c. into peripheral venous blood and the stage of clinical advancement of larynx cancer according to AJC. In patients with stage I and II of clinical advancement of this disease (examined jointly — Fig. 1) the occurrence of f.t.c. in peripheral venous blood was found in 20% of the examined persons, in patients with stage III of clinical advancement f.t.c. were found in 67% of the examined persons, and in 78% of patients with stage IV. The statistical analysis of these results showed a highly significant relationship between the frequency of f.t.c. occurrence in venous blood in the group studied and the increase of the stage of clinical advancement of laryngeal cancer classified according to AJC ($x^2=14{,}32$; $P<0{,}001$).

Dissemination of f.t.c. into peripheral venous blood and clinical evaluation of the feature T (according to A.J.C.) in laryngeal cancer. In patients with the feature T_1 and T_2 of tumor infiltration, which were examined jointly (Fig. 1), f.t.c. in venous blood were not found in any of 8 persons examined, whereas they were found in 63% of the examined persons with the infiltration feature T_3, and as high as in 84% of those examined with the cancer infiltration feature T_4. The statistical analysis of these results showed a still higher significance (than previously in relation to clinical gradation) in the group studied between the frequency of f.t.c. occurrence in peripheral venous blood and advancement of the infiltration feature T in laryngeal cancer according to AJC ($x^2=16{,}94$; $P<0{,}001$).

Though only two levels of determinations: "+" (1—5 f.t.c. in a sample) and "++" (5—10 f.t.c. in a sample, rarely more) were used in the descriptive interpretation of the investigation results, as the number of f.t.c. found did not usually exceed these levels, in 5 persons of this group, however, more than 10 f.t.c. were observed in the preparations examined, and in 2 of them the number of f.t.c. before death could be compared to "a shower of cancer cells", as described by some authors. Such a number of cancer cells (beside these two patients) was observed only in deaths in the model group. These few high determinations (above 10 f.t.c. in a sample) concerned only one patient out of 62 requiring radical treatment (surgical or irradiation) and belonging to group 9, and as many as 4 persons out of 16 patients were not qualified for radical treatment and also belonging to group A. The history of the further survival of 5 patients out of 78 persons examined (group A) in which such a high level of f.t.c. was found is as follows: three of the patients died up to 18 months after treatment, two, patients lived after treatment with symptoms of clinical recurrence and the presence of f.t.c. in venous blood and only one patient of this group lived after an operation without symptoms of cancer recurrence and without the presence of f.t.c. in venous blood.

It would follow from the present observations of this group (A) of patients studied, necessarily limited because of a short period of treatment, that no evident relationship between the clinical condition of the patients after the applied treatment of the cancer and the presence of f.t.c. in the blood before their treatment was found, except or those patients who were qualified for radical treatment according to the present cryteria used.

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EXPLANATION OF FIGURES

Fig. 2a. Squamous cell carcinoma of the larynx (patient Z. J. 45 years old, register No.1514/71). Smear from the tumour. A clump of desquamated cancer cells with preserved shapes, shows orange-red fluorescence of the cytoplasm and yellow fluorescence of large excentrically located nuclei with irregular system of chromatin. 600x.

Fig. 2b. Squamous cell carcinoma of the larynx (the same patient). Smear from the tumour. Single desquamated cancer cells (spinocellular type) fluorescence typicall for cancer cells. 600x.

Fig. 2c. Squamous cell carcinoma of the larynx (the same patient). Condensed blood from the cubital vein. Round (one large and two small) cancer cells show of lively-red fluorescence of the cytoplasm. Large nuclei of irregular system of chromatin, excentrically located in smaller cells, fluorescence yellowish. 600x.

Fig. 3. Cancer of the pancreas. Condensed blood from the right chamber of the heart. A large cancer cell. Bright-orange intensive fluorescence of the cytoplasm overshadows the fluorescence of the cell nucleus the contours of which are slightly visible. 600x.

STRESZCZENIE

Badania kliniczne i laboratoryjne przeprowadzono w grupie 78 chorych (grupa A) u których poszukiwano w.k.n. w krwi żylnej obwodowej przed pierwszym leczeniem nowotworu; w grupie 45 chorych (grupa B), u których poszukiwano w.k.n. w krwi żylnej obwodowej przed leczeniem operacyjnym (całkowitym wycięciu krtani), w krwi żylnej drenującej w czasie operacji i w krwi żylnej obwodowej w 5—7 dobie po operacji; oraz w grupie 40 osób (grupa C) badanych w okresie od 1 roku

do 5 lat po operacyjnym leczeniu raka krtani. W użytych metodach badań laboratoryjnych stosowałem technikę izolowania i koncentracji w.k.n. w krwi podaną przez Malmgrena i wsp. w modyfikacji Longa i wsp. Preparaty barwiono oranżem akrydynowym metodą opisaną przez Bertalanffy'ego, a oglądano w zestawie mikroskopowym cytofluorescencyjnym firmy Zeissa. Dla kontroli zastosowanych metod badawczych przeprowadzono badania modelowe u 10 osób zmarłych w wyniku rozsianego procesu nowotworowego (raka) różnych narządów (kontrola modelu barwienia i oceny diagnostycznej w.k.n.), badania eksperymentalne wg Schrecka w grupie 10 osób zdrowych (kontrola techniki izolowania i koncentracji) oraz badania kontrolne w grupie 25 osób zdrowych — wolnych od nowotworu — jako kontrolę diagnostyczną prawidłowego obrazu krwi i tzw. komórek atypowych krwi. Dane liczbowe uzyskane z przeprowadzonych badań klinicznych i laboratoryjnych opracowano statystycznie. Przedstawiono wyniki badań na obecność w.k.n. w krwi 78 chorych na raka krtani — grupa A przed pierwszym leczeniem nowotworu.

РЕЗЮМЕ

Исследовано кровь больных раком гортани на предмет наличия в крови свободных клеток опухоли (с.к.о.) и их значения. Клинические и лабораторные исследования проводились в группе из 78 больных (группа А), у них с.к.о. искали в венозной периферической крови перед началом лечения вообще, в группе из 45 больных (группа Б), у которых старались обнаружит с.к.о. в венозной периферической крови перед началом хирургического лечения, в венозной дренирующей крови — во время операции и в венозной циркулирующей крови — 5—7 сутки после операции, также в группе из 40 человек (группа Ц) исследовавшихся в течение 1 года — 5 лет после хирургического лечения рака гортани. Метод, по которому проводились лабораторные исследования, использовался мною с применением техники изолирования и концентрации с.к.о. в крови приведенной Malmgren и сотрудниками и модифицированную Longa и сотрудниками. Препараты окрашивались акрилинным метилоранжем по методу, описанному Bertalantty, а рассматривались в цитофлюоресцентрации с.к.о. в крови приведенной Malmgren и сотрудниками и модифицирометодов исследования, мною были проведены модальные исследования на 10 покойниках умерших в результате рассеянного опухолевого процесса (рака) в разных органах, (контролирование модели окрашивания и диагноза с.к.о.) экспериментальные исследования по Schreck (в группе из 10 здоровых людей) (контроль техники изолирования и концентрации), контрольные исследования в группе из 25 здоровых людей, не имеющих опухолей — в качестве диагнозного контроля правильности каотины крови и так называемых атипичных кровяных клеток. Количественные данные, полученные в результате проведенных клинических и лабораторных исследований обрабатывались статистически. Представлено результаты исследований на наличие с.к.о. в крови 78 больных раком гортани — группа А.

Fig. 2a

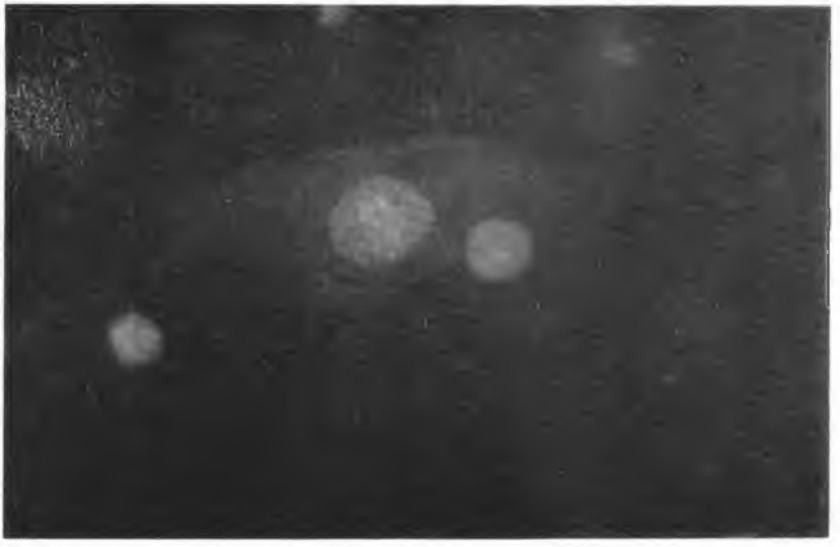

Fig. 2b

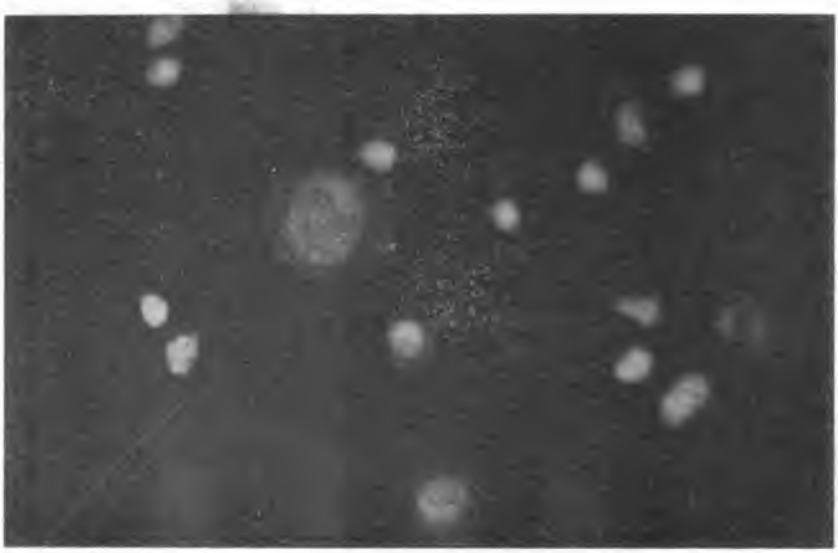

Fig. 2c

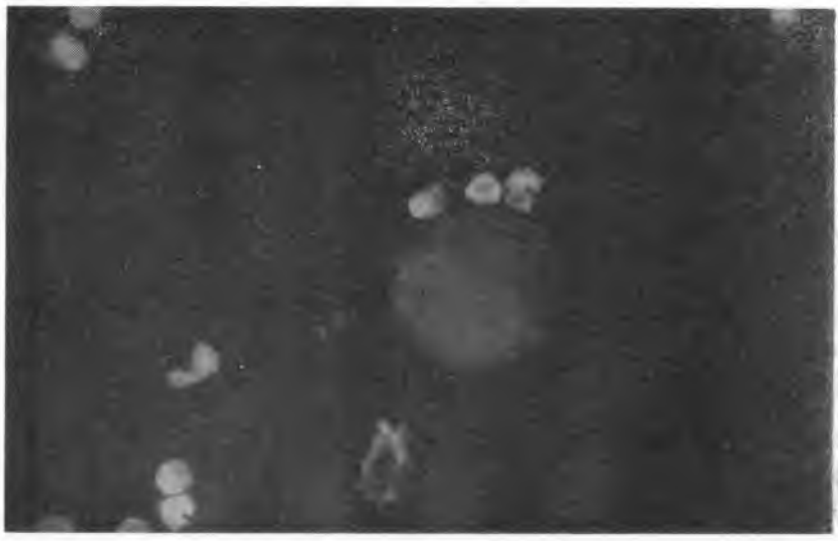

Fig. 3