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DELAYED CHANGES IN THE GROWING ORGANISM FOLLOWING SMALL RADIATION DOSES

by

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The study of delayed changes in the growing organism following small radiation doses may offer some new findings in the sphere of clinical radiobiology. Some time ago a preliminary report was published (STAŠEK et coll. 1962) on the results of examining a group of children irradiated early in life for benign conditions. This work has been continued and extended to include further irradiated children and a non-irradiated control group. The results of the examinations have been re-evaluated and an analysis of the material by a statistical method and dosimetric evaluation has been made. The results are now presented.

Material and Methods. The material consists of children irradiated during the period 1946 to 1951 for cervical lymphadenitis (72 cases) and hyperplasia of the thymus (5 cases). The ages at the time of treatment ranged from 2 months

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to 10 years. The controls on the 77 subjects took place from 10 to 15 years from the time of therapy; a control group of 106 untreated subjects were also examined.

Irradiation factors: Siemens bomb apparatus, fields 6 × 8 cm and 10 × 30 cm, FSD, HVL 0.2 to 0.8 mm Cu, mA 10, kV 120 to 160, dose rate 40 to 44 r/min; irradiation mainly fractionated usually with doses of 10 r to 50 r to the surface at 1 to 2 day intervals, the total surface doses being most frequently of the order of 125 r to 300 r. The total doses when higher were administered in a greater number of courses with intervals of several weeks or months. The applicator was adjusted so that the area of cervical lymph node involvement was included. The thyroid gland, larynx, pharynx, cervical spine, mandible, clavicle and sternal manubrium were, according to the technique used, either in the direct beam of irradiation or in its vicinity. It can be assumed that in children up to six months old the thymus was also directly irradiated, because at this age the gland is placed physiologically high up and reaches into the thoracic inlet (VALKER 1959).

With the irradiation technique used, a response in all tissues and organs of the irradiated area and an occasional general reaction were to be expected. The investigation was therefore divided into four main sections, each being carried out by the same members of the team throughout.

1. *Radiotherapeutic investigation.* Attention was directed to radiation changes in the skin, the other soft tissues of the neck, face and oral cavities. The history of the orginal condition was determined and any further exposure recorded.

2. *Ear, nose and throat examination.* A complete ENT examination, including anterior and posterior rhinoscopy, examination of the oral cavity, throat and tonsils, indirect laryngoscopy and diaphanoscopy were performed; phoniatric and histologic examinations were carried out where necessary.

3. *Roentgen examination.* Examination of the cervical spine, mandible and larynx, and sometimes of the facial bones, teeth and thoracic inlet were also performed.

4. *Pediatric examination.* The complete clinical examinations included basic biochemical values of the blood. The characteristics that are dependent in their development mainly on the functional influence of the endocrine glands within the irradiated area were followed. A search was also made for other signs that might reveal any condition resembling damage connected with irradiation.

Results

A. The irradiated group

Since the doses applied were low, and the irradiation fractionated, it was probable that delayed changes, if they appeared at all, would be slight. Since changes of this type may have a non-specific character (DUNLAP 1957) it was necessary, in evaluating the findings and in examining them critically from the viewpoint of causal connection, to consider all pathogenic factors as well as the radiation exposure. The patients were accordingly divided into two main categories.

The first category consisted of subjects in a normal state of health. Those with pathologic conditions, in whom a definite further pathogenic factor was present in addition to that of irradiation, were also included. The findings in this category were marked negative.

The second category consisted of 45 subjects in whom pathologic conditions were diagnosed and no additional pathogenic factor could be determined. The findings in this category consisted of (1) changes in the tissues and organs within the irradiated area, (2) the presence of systemic disorders, and (3) evidence of tumours. These were marked positive.

1. *Changes in the tissues and organs within the irradiated area* were diagnosed in 41 subjects. An abnormal degree of dental decay with numerous periapical granulomas mostly affecting the lower jaw (in three); facial asymmetry with unilateral mandibular hypoplasia (in three); changes in the cervical spine (alteration of bone structure, thinning of the intervertebral discs, marginal osteophytes) (in 25 cases); definite atrophy of the mucous membranes of the pharynx and the laryngeal aperture, combined with dryness of the mucous membranes and accompanying dilation of capillaries or groups of capillaries (in 23 cases); asymmetry of the larynx with normal functioning of the vocal cords (1 case).

2. *Systemic disorders were diagnosed in 14 subjects.* Dysmenorrhea in a 14-year-old girl: metrorrhagia in a 11-year-old girl; considerably delayed development of secondary sexual signs in a 19-year-old girl; hypogenitalism and subnormal general development in 3 boys; an adiposogenital type of development in 4 boys, in one connected with marked psychic retardation; obesity with premature development of secondary sexual signs in one boy; and gynecomastia in 3 boys, unilateral in one and bilateral in the other two.

3. *Tumours* were diagnosed in 3 irradiated subjects, i. e. in two adolescents 14 years after exposure and in one girl who died 8 1/2 years after irradiation for benign cervical lymphadenitis. Papilloma of the anterior palate arch was discovered in a 14-year-old girl and histologically confirmed as a benign papilloma. Carcinoma of the thyroid gland with metastases to the cervical lymph node was present in a 14-year-old boy. An ovarian tumour was discovered in a 12-year-old girl and laparotomy revealed metastases in the abdominal organs and ascites. Seminoma of the ovarium, teratogenic type, was histologically proved. Autopsy disclosed metastases in the pelvic and abdominal organs as well as in the spine.

B. The control group

There were 106 subjects in the control group and, by the same examination method as was used for the irradiated group, 98 were found to be physically normal. Thinning of the cervical intervertebral disks of the cervical spine, with no other changes in the skeleton, was present in 5 subjects. In 3 subjects, systemic disorders were found: in two boys these consisted of an adiposogenital type of development and in one abnormal obesity, distinctly marked in the area of the mammary glands.

Evaluation of the findings

1. *Roentgen diagnosis.* The search for and evaluation of radiation changes in bones had to be conducted over the entire area that might have been exposed to irradiation. Decreased volume and flattening of the mandible, leading to asymmetry of the facial skeleton accompanied by slight structural changes in the cervical vertebrae, was observed in 3 cases. No advanced spinal changes, such as belong to the higher degree of radiation damage to a growing spine (asymmetry and wedge-shaped deformation of the vertebrae with irregular contours and scoliosis) (SARRAZIN et coll. 1961), were evident in the irradiated group. Slight alteration in the bone structure of the vertebral bodies, accompanied by changes in the mandible, were seen in 25 irradiated children. These structural changes appeared as hypertrophic porosis with accentuated width of the bone trabeculae, and with so-called growth lines, i. e. fine dense strands, running transversally through the vertebrae parallel to their margins. These appearances are manifestations of retardation of bone growth equalized at a later period; this retardation is non-specific and usually accompanies all serious conditions of general ill health in children. Similar structural changes in the spine were not, however, evident in the control group. A decrease in

the thickness of the intervertebral disks and structural changes were present in the irradiated group. Five children of the control group, however, also had narrowed intervertebral disks so that this sign may not be of significance. At the same time it was noted that two of the irradiated children had osteophytes of the vertebral bodies posteriorly in the affected joints whereas these were absent in the control group.

Calcification of the laryngeal cartilages became visible only after the age of 18 years. There was no proof that this was more premature or marked in the irradiated than in the control group.

2. *ENT diagnosis.* The aim was to determine the condition of the mucous membrane of the oral cavity, pharynx and larynx in the patients who had been irradiated in early childhood and in the control group. The significance of the changes in relation to general health was considered.

The ENT case histories revealed previous illnesses with their frequency and length of duration. In evaluating the results of the examination the following were regarded as negative: signs of focal infections with adenoidal vegetation, obstruction of the nares, or chronic tonsillitis with pus or debris. Adolescents with symptoms of acute inflammation of the respiratory tract, who did not present themselves for examination after the conclusion of an attack, were included, i. e. 9 subjects in the irradiated group. In diagnosing the findings a satisfactory differentiation between changes caused by chronic or acute inflammation and those caused by radiation was found to be impossible because it was recognized that some of the changes produced by the latter may be similar to those that occur after tonsillectomy (thinning of the mucous membrane, reduced moistness); the findings in the tonsillectomy patients were also considered negative. Of the 33 tonsillectomy patients examined, 15 belonged to the irradiated group and 18 to the control. The operation in the irradiated group had not been followed by haemorrhage, and healing had occurred within the normal period. Thinning of the mucous membrane and reduced moistness of the throat was sometimes observed and occasionally dilation of the capillaries.

Thinning of the mucous membrane of the pharynx or laryngeal aperture was evident in 15 subjects of the irradiated group and in some was accompanied by a reduction in its moistness. These changes do not necessarily indicate delayed radiation changes as they may be found in non-irradiated subjects as well; they were present in 6 subjects of the control group.

Twenty-three adolescents of the irradiated group had marked thinning and atrophy of the mucous membrane of the pharynx or laryngeal aperture and an increase in the number of dilated capillaries or groups of capillaries. These

changes were often present in unusual areas: the epiglottis, pharyngoepiglottal folds and piriform sinuses. They were not found in the control group.

Asymmetry of the larynx, with normal functioning of the vocal cords, was evident in one irradiated girl, and a papilloma on the anterior arch of the palate histologically confirmed as benign in another girl. These changes were additional to those mentioned above.

Chronic atrophy of the pharynx and respiratory tract lowers the protective resistance to various harmful influences likely to be encountered when these adolescents come into working conditions on reaching maturity or begin to smoke. Atrophic changes in the pharynx may after some years even affect the condition of the respiratory tract. The epithelium, glands and mucous capillaries and all their functions are damaged and future control examinations may give an indication of the eventual effects of the initial trauma.

3. *Clinical examinations.* The pediatric examination served as a basis for evaluating the influence of irradiation on the general development of the subjects, and because so many significant endocrine glands, e. g. the thyroid, thymus and pituitary, lay within the irradiated area it could be assumed that growth deviations would occur. The situation is rendered more difficult as these three glands may exert a broad influence on development e. g. psychic and sexual development, or indirectly guide more restricted fields of growth through their influence on the other endocrine glands. Most of these children were irradiated either as infants or toddlers whereas the examinations were carried out at times when the most complicated and unsettled period of development is to be expected, i. e. puberty. In view of the variability which characterizes the period of puberty in the broadest sense of the word, the final evaluation of deviations was not easy.

With one exception there was no family history of endocrine or psychic disturbances. Evaluation of general development was made according to the height and weight, which were compared with the Czechoslovak all-state norms ("Tables published by the Ministry of Health on the basis of a somatometrical investigation carried out by the Anthropological Commission, Prague 1951."). Height was considered with due regard to age and weight, secondarily in relation to height, so that any somatic disproportion between height and weight was evident. The general development in the irradiated group did not differ from that in the control group. The chest and abdominal organs were either within physiologic limits, or the changes found could not be correlated with irradiation.

Biochemical data were recorded for blood proteins, non-protein nitrogen, cholesterol, sodium, potassium, calcium, phosphorus, and alkaline phosphatase.

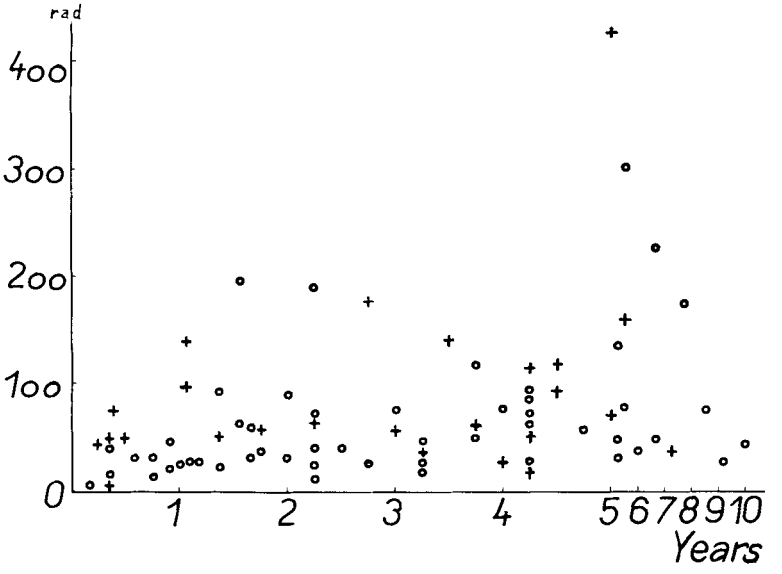

Fig. 1. Doses absorbed in cervical spine area in individual cases, converted to equivalent single dose radiation. Positive finding + negative ○.

The results corresponded to the medium values for the given ages. In so far as isolated minor deviations appeared, they were not significant.

Fourteen subjects in the irradiated group presented evidence of greater or smaller deviations that could be explained by disturbed functioning of the endocrine system.

Dysfunction of the glands, controlling sexual development and secreting growth hormone, was apparent in 3 girls. Assuming an etiopathogenetic dependence of the origin of these disturbances on radiation, then in two of the girls (dysmenorrhea, metrorrhagia) the effect could be considered rather as a stimulatory one and in the third girl (considerably delayed development of secondary sexual signs and general hypotrophy) as an inhibitory effect, both as regards sexual maturing and the effect on growth.

The largest group consisted of 7 boys in whom delayed sexual development was diagnosed. Hypogenitalism accompanied by subnormal general development, i. e. marked general hypotrophy was present in three of these, and the adiposogenital type of development was common to the other four boys, in one of them accompanied by marked psychic retardation.

Incidence of gynecomastia was demonstrable in 3 boys, unilateral in two and bilateral in one boy. The nipples protruded and were broadly cone-shaped;

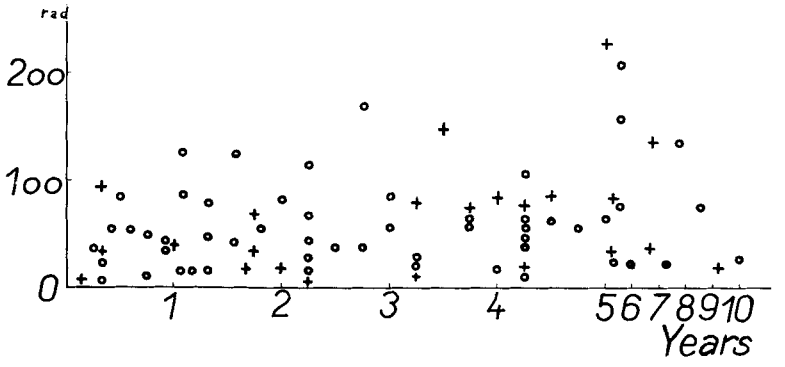

Fig. 2. Doses absorbed in the larynx area in individual cases, converted to equivalent single dose radiation. Positive finding + negative ○.

typical glandular disk formation was evident in the area of the nipples. Gynecomastia is known to occur commonly in endocrine disorders (TREVES 1958).

The most significant diagnosis was made in one boy. He had been subjected to irradiation for bilateral cervical lymphadenitis at the age of 5, and a total dose of 420 r, fractionated over a period of 5 weeks, had been administered. At the age of 14, a cervical node was extirpated, in which metastases of cancer of the thyroid gland were histologically verified. The tumour was mainly cystopapillary in structure, in parts containing macrofollicular formations with colloid, and in others a more microfollicular to solid formation. Subtotal strumectomy was also performed. Histologic examination revealed the tumour structure to be the same as the metastases. There were signs of endocrine stigmatisation — some obesity and premature development of secondary sexual signs. The boy is at present under treatment at the endocrinologic institute.

Two boys in the control group had evidence of an adiposogenital type of development, one of them in the form of abnormal obesity, which was more strikingly marked in the chest, especially in the area of the breasts.

No characteristic signs of radiation damage were present in any of the subjects. Non-specific deviations, indicating endocrine unbalance, were apparent, it is true, and of course radiation cannot be ignored as one of the possible etiopathogenetic factors. The supposition is admissible that the irradiation of endocrine glands in early childhood left a latent trace and later appeared in puberty as signs of endocrine unbalance. It was thought that a statistical-mathematical evaluation of the frequency of the observed findings, and a dosimetrical analysis of the applied doses, might help to clarify this question.

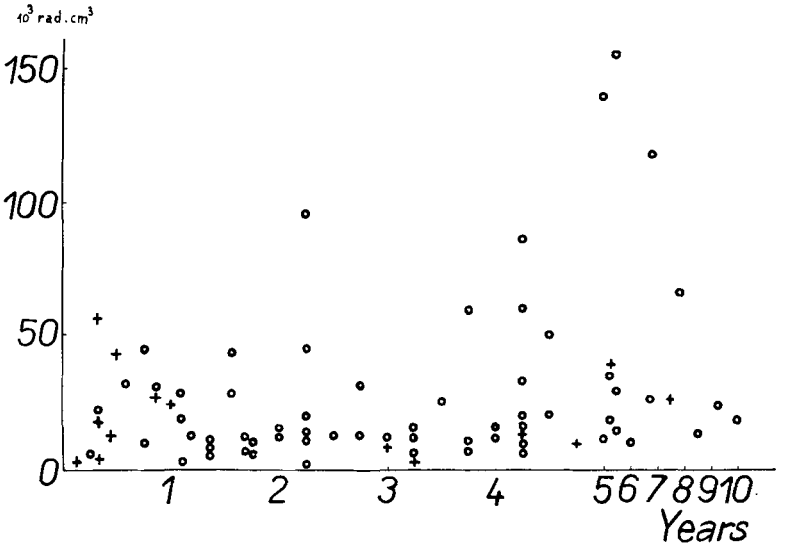

Fig. 3. Volume doses in individual cases, converted to equivalent single dose radiation. System deviation + physiological finding ○.

Statistical analysis. The statistical evaluation was approached with the knowledge that it is impossible to find an ideal control group that would correspond to the irradiated group. A random selection for the control group was therefore made. The aim of the statistical evaluation was to discover whether the difference between the frequency of positive findings in the irradiated group and that of the control group was significant. Although all types of verified findings, including some of the less numerous, are contained in the records, only those occurring with a frequency capable of statistical treatment were admitted for analysis. Changes in the cervical spine and in the mucous membrane of pharynx as well as systemic disorders were present in the material.

The statistical evaluation was carried out as follows: a four-fold table was worked out for each age group, the exact value of P was calculated, and the values obtained were combined for all age groups with the help of the χ^2-test. It emerged that the difference in frequency of the three types of findings mentioned is statistically significant — for system deviations at a 5 per cent level and for cervical spine changes and mucous membrane changes at a one per cent level of significance.

Dosimetric analysis. The result of the statistical analysis led to an investigation of whether it would be possible to establish, at least in general terms,

Table 1

Age group (years)	No. of irradiated children	Cervical spine			Larynx			Average volume dose rad cm³	Percentage of children with system deviation	Frequency of system deviation per volume dose 10^4 rad cm³ %
		Average dose (rad)	Percentage of children with positive finding	Frequency of positive findings per dose 25 rad %	Average dose (rad)	Percentage of children with positive finding	Frequency of positive findings per dose 25 rad %			
0—1/2	7	32.3	57.1	44.2	35.3	42.8	30.4	17 650	71.4	40.4
1/2—1	7	16.7	14.3	21.4	44.7	14.3	8.0	30 700	28.6	9.3
1—2	15	63.3	26.7	10.5	54.6	26.6	12.2	14 100	0	0
2—3	11	68.6	27.3	10.0	58.5	9.1	3.9	22 500	9.1	4 0
3—4	10	59.1	40.0	16.9	58.5	50.0	21.3	15 800	10.0	6.3
4—5	13	98.0	53.8	13.9	69.1	30.8	11.1	36 300	18.2	5.0
5—10	14	101.2	14.3	3.5	74.2	35.7	12.0	42 000	14.3	3.4

a relation between the occurrence of the changes and the age at the time of exposure, and whether the biologic effect could be related to the applied dose.

The average absorbed dose in the cervical spine area and larynx was first determined in each child. It was also found useful to determine the volume dose. The surface doses and the irradiation technique used were considered for this purpose. In view of the considerable differences in the length and number of irradiation courses, it was also necessary to take into consideration the time factor. An equivalent absorbed dose was therefore calculated which should have the same biologic effect in single dose radiation. STRANDQVIST's (1944) nomogram was used. The equivalent absorbed doses in the cervical spine area and larynx in individual subjects, divided according to age, are shown in Figs 1 and 2. Fig. 3 gives the volume doses, which are also converted to single doses with the equivalent biologic effect. If the correctness of the linear dependence between the dose and biologic effect, expressed by the positive findings (BEACH et coll. 1962, HAMILTON 1963) be assumed, the question formulated at the beginning of this section may be answered. The data are collected in the Table.

The irradiated children were divided into 7 groups according to age at the time of exposure. An average equivalent dose and the frequency of positive findings in the cervical spine and larynx area were determined for each group. In assuming the proportionality, the percentage of positive findings, corresponding to the equivalent absorbed dose of 25 rad, was determined. The fre-

quency of systemic disorders, corresponding to the equivalent dose of 10^4 rad cm^3, was similarly calculated.

The results reveal that in children irradiated before they reach the age of one year the frequency of positive findings or of systemic deviations was, for the same dose, considerably higher than in older children. The values shown in the Table even indicate that in children under one year of age the frequency of findings indicates a marked increase with decreasing age.

As to the second question, it may be assumed that from the material it may be possible to find at least a general relation between the absorbed dose and the frequency of the findings in the cervical spine and laryngeal area. The question demands a separate theoretical and detailed statistical study.

Conclusions

A group of 77 children irradiated in early childhood for benign conditions were examined 10 to 15 years after exposure. A control group of 106 children and adolescents was also examined. Local changes in the tissues and organs and systemic disorders were revealed in both groups and tumours were also discovered in the irradiated group.

Changes in the cervical spine were characterized in the irradiated group by alteration in the bone structure of the vertebral bodies, signs of osteophytes posteriorly, and diminution in the thickness of the intervertebral disks. These changes accompany all more serious disturbances leading to temporarily retarded growth in children and are therefore non-specific. Only degeneration of the intervertebral disks in the area of the cervical spine was found in 5 adolescents of the control group.

More marked changes in the irradiated group were observed in the lower jaw. These appeared as a decrease in size, and unilateral flattening of the mandible which led to facial asymmetry. They were accompanied by abnormal dental decay and the formation of periapical granulomas.

Thinning of the mucous membrane of the pharynx and laryngeal aperture combined with reduced moistness may be observed in those who have not been exposed to irradiation. It is, however, considerably rarer in young subjects than in adults. In 23 subjects of the present series, who were exposed to radiation, the condition was especially marked, for, in addition to atrophy and dryness of the mucous membrane, capillaries, or groups of capillaries, were found to be dilated. These lay not only in the pharynx but also in the epiglottis, pharyngoepiglottical folds, valleculae, and piriform sinuses. These changes did not occur in the control group.

The difference in the frequency of all the findings in the two groups was significant statistically, i. e. at a one per cent level of significance.

As with the local tissue and organ changes, systemic disorders were in the nature of non-specific disturbances probably referable to the endocrine glands. The thyroid, thymus and pituitary glands were in the direct beam of radiation or in its vicinity. These are endocrine glands that can exert a direct general influence on growth, e. g. on psychic and sexual development, or indirectly guide more restricted fields of development by influencing the other endocrine glands with which they are in correlation. Irradiation in the present material was carried out in early childhood, i. e. at the time when these glands were still for the most part quiescent. With the statistical significance — at the five per cent level — of systemic disorders it would be possible to assume that radiation had left latent traces of damage to the organs manifest at puberty.

The frequency of tumours in 3 subjects of the irradiated group, cancer of the thyroid gland, benign papilloma of the palate arch and an ovarian seminoma, is beyond the range of statistical evaluation and no conclusion can be drawn as to its relation to radiation as a pathogenic factor.

No clinical signs of radiation changes in the skin were found, although it was subjected to a higher radiation dose than the other organs. It may be possible to explain this by the fact that the skin of children possesses a greater reparative capacity than the other organs under consideration in the area of the neck.

In view of the fact that the difference between the frequency of the tissue and organ changes and systemic disorders in the irradiated group and that of the control group was statistically significant, or very significant, it is assumed that radiation acted as an important pathogenic factor. Even small doses of radiation are undoubtedly not harmless for the growing organism. The authors therefore consider that it would be advisable to revise from this point of view the use of ionizing radiation in the treatment of benign conditions in children and adolescents.

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SUMMARY

A group of 77 subjects irradiated in early childhood for benign conditions were examined 10 to 15 years later, a group of 106 patients acting as a control. In view of the fact that the difference between the frequency of tissue and organ changes and systemic disorders in the irradiated group and that of the control group was statistically significant or very significant, it is assumed that radiation acted as an important pathogenic factor.

ZUSAMMENFASSUNG

Eine Gruppe von 77 Personen, die im frühen Kindesalter für gutartige Erkrankungen röntgenbestrahlt worden waren, wurden 10 bis 15 Jahre später untersucht, eine Gruppe von 106 Personen diente zum Vergleich. In Anbetracht der Tatsache dass Gewebe- und Organveränderungen und Systemerkrankungen nach Bestrahlung in statistisch bedeutsamer Weise häufiger gefunden wurden als bei der Kontrollgruppe, muss angenommen werden, dass Bestrahlung ein wichtiger pathogener Faktor ist.

RÉSUMÉ

Un groupe de 77 sujets irradiés dans leur jeune enfance pour des affections bénignes ont été examinés 10 à 15 ans plus tard et comparés à un groupe de 106 sujets témoins. Etant donné que la différence entre la fréquence des lésions de tissus et d'organes et les troubles systémiques chez les sujets irradiés et chez les sujets témoins est statistiquement significative ou très significative, les auteurs admettent que l'irradiation a eu un rôle pathogénique important.

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