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SERUM AUTOANTIBODIES IN ATOMIC BOMB SURVIVORS, HIROSHIMA AND NAGASAKI

原 爆 被 爆 者 に お け る 血 清 自 己 抗 体 の 調 査,
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In the continued interest of accurately defining the late effects of the atomic bombs, the qualitative and quantitative characteristics of the A-bomb radiation exposure doses are periodically refined. If warranted by future dose assessments, the data reported here will be reanalyzed and subsequently reported.

原爆の後影響を引き続いて正確に究明する目的をもって，原爆放射線被曝線量の質的・量的特質について定期的に改良を加えている．今後線量評価によって，その必要性が起これば，本報の資料を再解析の上，改めて報告する．

SERUM AUTOANTIBODIES IN ATOMIC BOMB SURVIVORS, HIROSHIMA AND NAGASAKI

原爆被爆者における血清自己抗体の調査, 広島及び長崎

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SUMMARY

In order to evaluate delayed effects of radiation on humoral immunity, an attempt was made to detect antibodies in the serum of atomic bomb survivors against kidney, liver, and parietal cells from rats. The following results were observed.

Comparing by sex and age, the detection frequency of antibodies increased significantly for all three organs in the male group only.

Analysis of changes in antibody·detection frequencies by age and exposure dose without considering sex showed that the rates for those exposed to 100+ rad showed a trend to increase with age for all three organs (P<0.01). However, in the 0 rad group, a significant trend to increase with age was noted for antikidney and antiliver antibodies only (P<0.01 for both).

Analysis of changes in antibody detection frequencies by sex, age, and exposure dose showed that the detection frequencies increased significantly with age for all three organs in males exposed to 100+ rad (P<0.05), but only the anti-

要 約

放射線の体液性免疫現象に及ぼす晩発影響の評価のために，ラットの腎・肝・胃壁細胞に対する原爆被爆者血清中の抗体の検出を試み，以下の結論を得た.

性及び年齢別に比較すると，三つの臓器すべてにおける抗体の検出頻度は，男性群においてのみ有意に上昇した.

性別を加味しないで年齢と被曝線量別に抗体検出頻度の変動を解析した場合，100rad 以上の被曝群の検出頻度は三つの臓器すべてに対して加齢に伴い上昇傾向を示した（ P < 0.01 ）. しかしながら，0 rad 群は抗腎・抗肝抗体に対してのみ加齢に伴う上昇の有意傾向を示した（両抗体とも P < 0.01 ）.

性，年齢及び被曝線量別に抗体検出率の変動を解析した場合，男性群における100rad 以上に被曝したグループでは，三つの臓器すべてに対して加齢に伴い検出頻度が有意に上昇した（ P < 0.05 ）. しかし

liver antibody frequency increased significantly with age in males in the 0 rad exposure group. Females failed to show any statistical changes in any exposure group.

INTRODUCTION

It has been demonstrated that transitory disorders occur in the immunologic mechanism as acute effects of radiation. There are also a large number of studies suggesting the development of immunologic dysfunction as a late effect of exposure to ionizing radiation. At present, it is unknown to what extent immunologic dysfunction exists in A-bomb survivors in Hiroshima and Nagasaki. If there is a long-term impairment of immunologic competence in A-bomb survivors, the consequences of this dysfunction would be serious from the viewpoint of oncogenesis, aging, resistance to infectious diseases, and development of autoimmune diseases.

With the aim of detecting late effects of radiation, a number of studies in the field of immunology have been and are being conducted on a study sample in Hiroshima and Nagasaki.[1-12] No correlation with radiation exposure has been found for the major erythrocyte antigens, parietal cell antibody, hepatitis-associated antigen and antibody, or serum antibody titer of EB virus antibody.[1-5] Recently, one of the research projects investigating the Adult Health Study (AHS) sample was expanded to clarify whether the HB antigen titer is excessively high in the group exposed to 100+ rad. The results obtained to date suggest possible radiation effects.[6] Serum immunoglobulin levels (IgG, IgA, and IgM) in A-bomb survivors were found to be within normal limits.[7] A study of the response of serum antibody to Asian influenza vaccine suggested impairment of antibody synthesis against one of the influenza viruses which was prevalent in Japan around 1945.[8]

Several types of antibodies have been found in the AHS sample.[2] However, the total frequency of antibodies in this sample, and its relationship with age, sex, and radiation exposure have remained unclear.

As part of a research project to assess delayed effects of radiation on humoral immunity, an attempt was made to detect various organ-specific antibodies in the serum of A-bomb

ながら，男性の0 rad 群では抗肝抗体のみが加齢に伴って有意に上昇した．女性群はいずれの被曝線量群においても統計学的な変動を示さなかった．

緒　言

放射線の急性影響として免疫機序に一過性の障害が生ずることは立証されている．また，電離放射線被曝の後影響として免疫機能障害の発生を示唆する研究も多数ある．しかし，広島及び長崎の原爆被爆者に現在どの程度の免疫機能障害があるかは不明である．原爆被爆者に長期的な免疫能の障害があるとすれば，その機能障害による影響は，腫瘍発生，加齢，感染症に対する抵抗，及び自己免疫疾患の発生という観点から極めて重大であろう．

放射線の後影響を探知するために，広島及び長崎の調査対象者について免疫学分野の研究が幾つか実施されている．[1-12] 主要な赤血球抗原，胃壁細胞抗体，肝炎関連抗原，抗体又はEBウイルス抗体の血清抗体価については，被曝との相関関係は認められていない．[1-5] HB抗原の力価が100 rad 以上の被曝群において過度に高いか否かを究明するために，最近成人健康調査集団を調査する研究計画の一つが拡大された．これまでに得られた結果から放射線影響の可能性が示唆されている．[6] 被爆者の血清免疫グロブリン値（IgG，IgA及びIgM）は正常範囲内にあった．[7] 血清抗体のアジア型インフルエンザ・ワクチンに対する反応調査から，1945年ごろ日本に流行したインフルエンザ・ウイルスの一つに対する抗体合成の障害が示唆された．[8]

成人健康調査集団に数種類の抗体の存在は認められている．[2] しかしながら，この集団中の抗体の総頻度，並びに年齢，性及び放射線被曝との関係はまだ不明である．

放射線の体液性免疫に及ぼす晩発影響を評価するための研究計画の一環として，原爆被爆者の血清における各種臓器特異抗体の検出を試みた．性，年齢

survivors. The results of the comparative study of the detection frequencies of these antibodies, conducted in relation to sex, age, and radiation exposure dose will be reported here.

及び放射線被曝線量との関連において実施された これらの抗体の検出頻度の比較研究の結果をここに 報告する.

MATERIALS AND METHODS

The base population for the antibody immuno-fluorescent assay consists of all A-bomb survivors exposed to 100 rad or more, who underwent the AHS examination cycle 9 (1974-76) in either city and whose plasma and serum specimens are cryopreserved. Their controls (0 rad group) were matched by age and sex (Table 1).

材料及び方法

抗体免疫蛍光検査の基盤集団は, 両市において成人 健康調査第9周期診察 (1974―76年) を受け, 血漿 及び血清標本が冷凍保存されている100rad 以上の 被爆者全員である. 対照者 (0 rad 群) は年齢, 性を 対応させた (表1).

TABLE 1 COMPOSITION OF STUDY POPULATION

表1　調査対象者の構成

Age at examination	Dose in rad	Male	Female	Total
<40	0	25	31	56
	100+	17	29	46
	Total	42	60	102
40-49	0	58	93	151
	100+	65	99	164
	Total	123	192	315
50-59	0	31	96	127
	100+	28	94	122
	Total	59	190	249
60-69	0	43	65	108
	100+	52	71	123
	Total	95	136	231
70+	0	42	59	101
	100+	39	52	91
	Total	81	111	192
	Total sample	400	689	1089

Immunofluorescence Method

Antikidney antibodies, antiliver antibodies, and antiparietal cell antibodies were detected by the immunofluorescence method. Kidney, liver, and stomach were removed from a rat and frozen by Cryoquick to form one block of the three organs. Then, the block of the three organs was sliced with a Cryostat, and mounted on a slide. The prepared tissue sections were placed in a wetting chamber, and one drop each of the undiluted serum was placed on the three-organ specimens and allowed to react at 37°C for

免疫蛍光法

免疫蛍光法によって, 抗腎抗体, 抗肝抗体, 抗胃壁 細胞抗体の検出を行った. ラットの腎, 肝, 胃を 切除し, 三つの臓器をそれぞれ一塊としてクリオ ックで冷凍した. これらの臓器の塊をクリオ スタットで薄く切断し, スライドに載せた. 用意した 組織切片を湿潤箱に入れ, 希釈していない血清を 1滴ずつ三つの臓器標本に落とし, 37°C で30～45分間

30-45 minutes, after which the sections were washed for 15 minutes in a phosphate buffer solution (PBS). After removal of the excess solution, they were again placed in the wetting chamber, and one drop of FITC-labeled anti-human IgG (antihuman IgG-FITC) was placed on each organ specimen, and incubated at 37°C for 30-45 minutes. After washing in PBS, the sections were embedded in glycerin and examined under a fluorescent microscope. Positive control serum obtained from a patient with systemic lupus erythematosus (SLE) was used as the standard of determination in each test.

The nucleus of liver cells dyed diffusely with SLE serum in the present experiment, while fluorescent staining was observed on a part of the cytoplasm as well as on the nucleus of parietal cells of the stomach and kidney cells. Serum which showed a similar stainability was assumed to be autoantibody-positive.

RESULTS
Antibody Detection Frequencies
The increasing trends of the detection frequencies for the antibodies corresponding to each organ are shown in relation to sex and age in Figure 1. When single regression analysis was applied to the age-specific detection frequencies for each organ and the trends of the regression coefficients were examined, a trend to increase with age was seen for all three organ antibodies. More particularly, in males this trend was significant for the three organs (kidney and stomach $P<0.01$, liver $P<0.05$).

Antibody Detection Frequencies in Relation to Exposure Dose
Males exposed to 100+rad showed a higher antibody detection frequency in all three organs, while the reverse was found to hold in females. Females in the 100+rad group showed a lower rate than the 0 rad group, but there was no significant difference in relation to sex by exposure dose. For sexes combined, the detection frequencies showed no significant difference between the 0 rad group and the 100+rad group (Table 2).

Antibody Detection Frequencies by Age and Exposure Dose
Since the detection frequencies for antibodies were found to increase with age as shown in

反応させ，その後その切片をリン酸塩緩衝液（PBS）で15分間洗浄した．余分な緩衝液を除いた後，再度湿潤箱に入れ FITC 標識抗ヒト IgG（抗ヒト IgG-FITC）を各臓器標本に1滴ずつ落とし，37°C で30～45分間培養した．リン酸塩緩衝液で切片を洗浄しグリセリンで包埋し，蛍光顕微鏡下で観察した．全身性紅斑性狼瘡（SLE）患者から得た陽性コントロール血清を各検査の規準の決定に使用した．

この実験においては全身性紅斑性狼瘡患者血清により肝細胞の核は瀰漫性に染色され，蛍光染色は胃壁細胞並びに腎細胞の核及び細胞質の一部にも認められた．同様の染色性をもつ血清は自己抗体が陽性であると考えた．

結 果
抗体の検出頻度
各臓器に対応する抗体の検出頻度の上昇の傾向を，性，年齢別に図1に示した．一次回帰分析を各臓器の年齢別検出頻度に適用し回帰係数の傾向を調べた場合，三つの臓器抗体すべてに年齢に伴う上昇傾向がみられた．特に男性群においては，この傾向が三つの臓器に対して有意であった（腎臓及び胃：P<0.01，肝臓：P<0.05）．

被曝線量別の抗体検出頻度
男性の100rad 以上被曝群では三つの臓器すべてにおける抗体検出頻度は高かったが，女性群においては逆の傾向がみられた．女性の100rad 以上被曝群は0 rad 群より低い検出頻度を示したが，性との関連で被曝線量別に有意な差異は認められなかった．両性を合わせた場合，0 rad 群と100rad 以上群の検出頻度には有意な差異はみられなかった（表2）．

年齢及び被曝線量別の抗体検出頻度
図1に示すとおり，加齢に伴い抗体の検出頻度が

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FIGURE 1 TRENDS OF DETECTION FREQUENCIES FOR ANTIBODIES IN SERUM BY SEX AND AGE
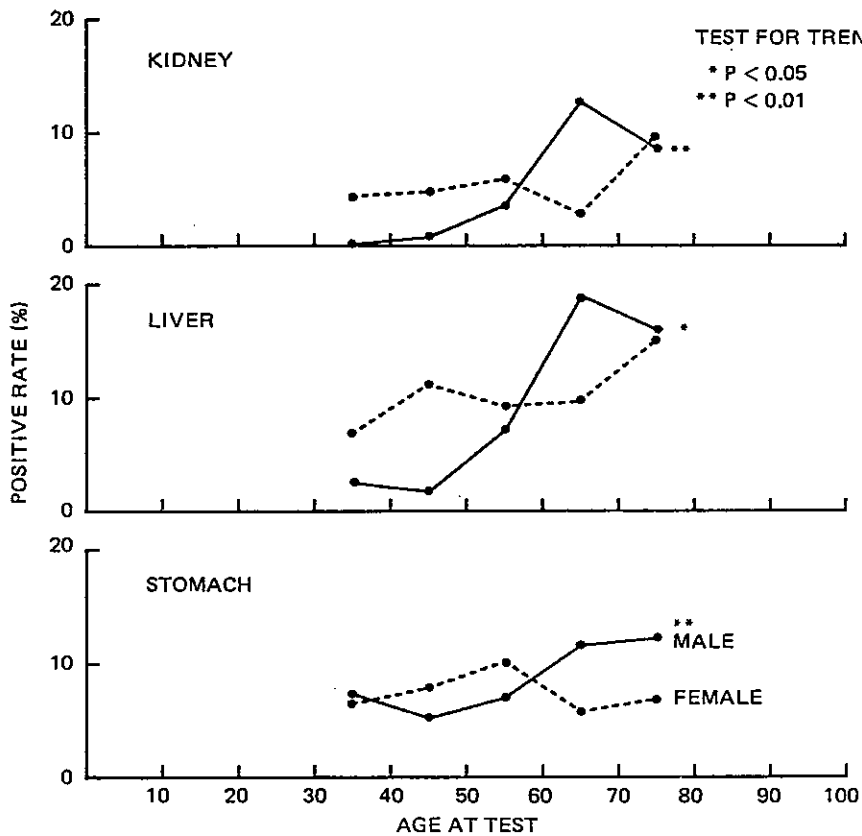
図 1 血清中抗体検出頻度の傾向，性及び年齢別

TABLE 2 DETECTION FREQUENCIES FOR ANTIBODIES IN SERUM BY SEX AND EXPOSURE DOSE

表 2 血清中抗体検出頻度，性及び被曝線量別

Organ	Dose in rad	Male		Female		Total	
		Number of specimens	Detection frequencies of possible cases	Number of specimens	Detection frequencies of possible cases	Number of specimens	Detection frequencies of possible cases
Kidney	0	196	4.59%	343	7.58%	539	6.49%
	100+	199	6.53	343	4.08	542	4.98
Liver	0	196	9.18	343	11.66	539	10.76
	100+	199	10.05	343	9.91	542	9.96
Stomach	0	196	7.14	343	9.04	539	8.35
	100+	199	10.05	343	7.29	542	8.30

FIGURE 2 TRENDS OF DETECTION FREQUENCIES FOR ANTIBODIES IN SERUM BY
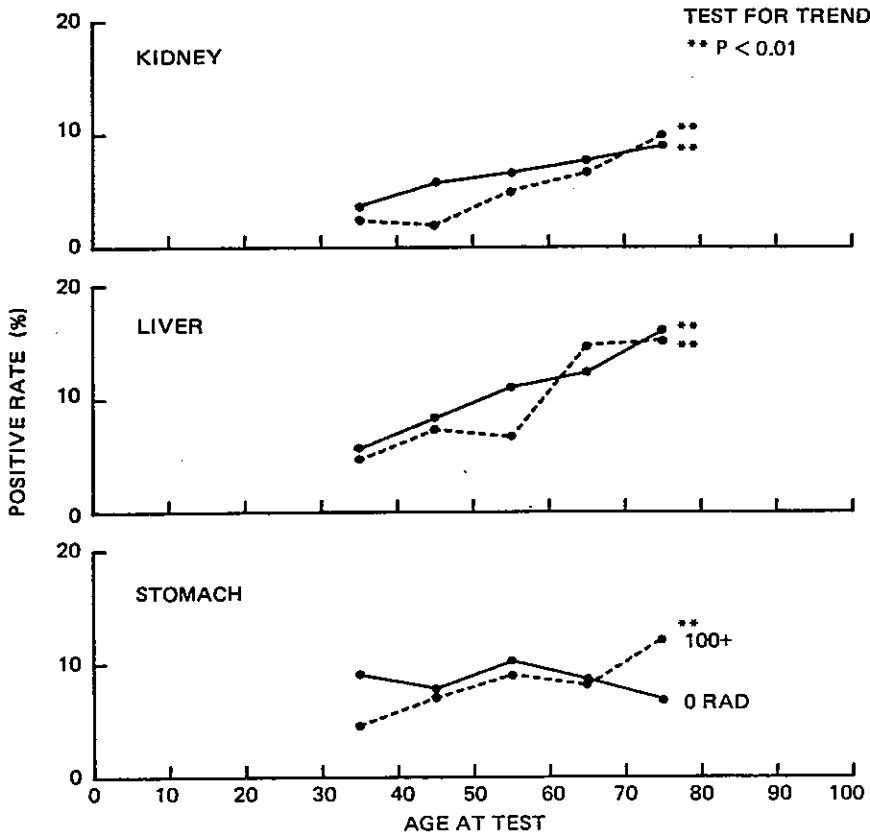AGE AND EXPOSURE DOSE
図 2　血清中抗体検出頻度の傾向，年齢及び被曝線量別

Figure 1, further analysis was conducted in relation to exposure dose and age. As indicated in Figure 2, the detection frequencies for antikidney and antiliver antibodies increased with age in both the 0 rad and the 100+ rad groups (P< 0.01). Although antigastric mucosa antibodies failed to show any definite changes in the detection frequency with age for the 0 rad group (P> 0.1), in the 100+ rad group there was a significant increase with age (P<0.01).

Antibody Detection Frequencies by Sex, Age, and Exposure Dose
The analysis of trends presented in Figure 3 was reviewed by sex, age, and exposure dose. Interestingly, the 100+rad group of males showed significant increasing trends in antibody detection frequencies with age for all organs (P<0.01). The 0 rad group showed a significant increase only for the liver (P<0.01). In females,

上昇することが認められたので，被曝線量と年齢別に更に詳細な解析を行った．図 2 に示すとおり，抗腎，抗肝抗体の検出頻度は 0 rad 及び100 rad 以上の両被曝群において加齢に伴い上昇した（P<0.01）．0 rad 群における抗胃粘膜抗体の検出頻度は加齢に伴う明確な変動を示さなかったが（P >0.1），100 rad 以上の被曝群においては加齢に伴い有意に上昇した（P<0.01）．

性，年齢及び被曝線量別の抗体検出頻度
図 3 に示す傾向の解析は，性，年齢及び被曝線量別に検討したものである．興味深いことに，a) 男性の100 rad 以上群の抗体検出頻度は，すべての臓器に加齢に伴う有意な上昇が認められた（P<0.01）．0 rad 群においては肝臓にのみ，有意な上昇を示した（P<0.01）．b) 女性群における抗体検出頻度の

FIGURE 3 TRENDS OF DETECTION FREQUENCIES FOR ANTIBODIES IN SERUM BY SEX, AGE, AND EXPOSURE DOSE
図3　血清中抗体検出頻度の傾向，性，年齢及び被曝線量別
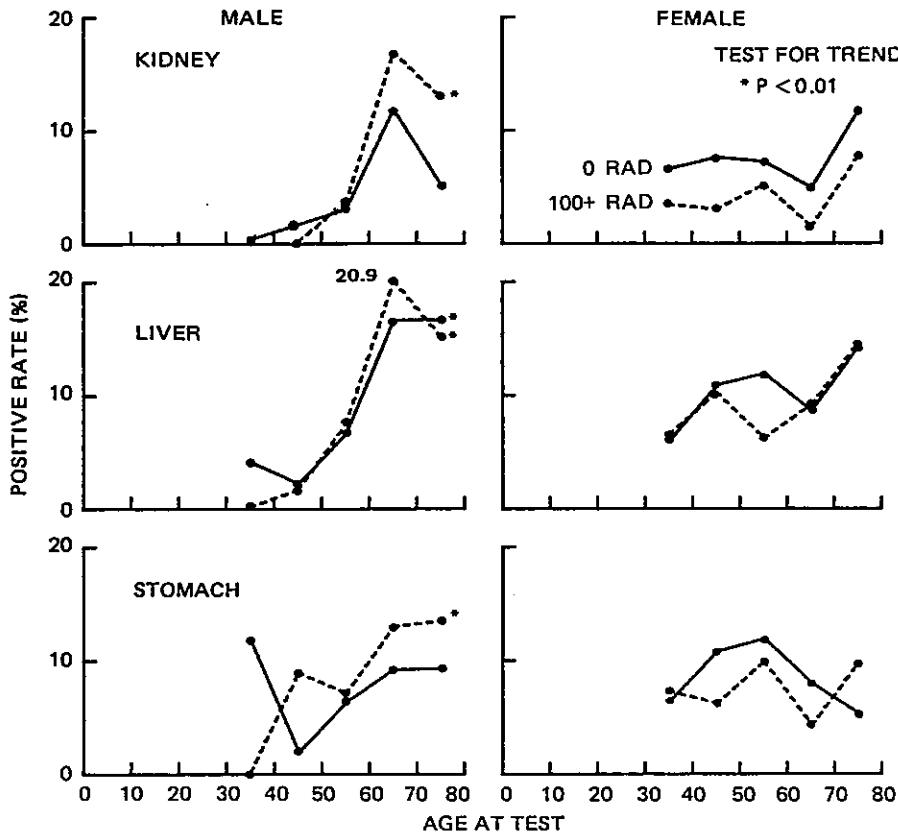
the increasing trends of antibody detection frequency with age were not statistically significant, despite differences in exposure data.

DISCUSSION
In order to evaluate the late effects of radiation exposure from an immunologic standpoint using serum specimens obtained from A-bomb survivors, the frequency of detecting antibodies was examined in relation to sex, age, and exposure dose. As a result, when viewed in relation to sex and age, the antibody detection frequencies showed a trend to increase with age for each organ used (kidney, liver, and stomach). This trend was especially clear in the case of males, but not in females. It is conjectured that this difference in the trend of detection frequencies between males and females may reflect certain effects occasioned by pregnancy in female groups.

加齢に伴う上昇傾向は，被曝データに差異が見られるにもかかわらず，統計的に有意ではなかった．

考　察
原爆被爆者から得た血清標本を使用し，免疫学的見地から放射線被曝の後影響を評価するために，性，年齢及び被曝線量別に抗体検出頻度を調べた．その結果，性及び年齢別にみると，抗体検出頻度は使用した各臓器，すなわち腎臓，肝臓及び胃に対して加齢に伴う上昇傾向を示した．この傾向は男性群の場合特に顕著であったが，女性群においてはそうでなかった．検出頻度における男女間のこの差異の傾向は，女性群の妊娠による何らかの影響を反映するものであろうと考えられる．

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In order to investigate the effects of A-bomb exposure, it is probably most reasonable to analyze the data on males. Among the male group exposed to 100+ rad, a significant increasing trend in antibody detection frequencies for all three organs has been observed with age, though the 0 rad group also showed a significant increasing trend for the liver.

It has been reported from animal experiments that both young and old persons whose T cell dependent-type immune activity is low are susceptible to the long-term effects of radiation.[13-16] There are few reports dealing with this matter in humans, either at the whole body or cellular level. There is only a report resulting from experiments by the present investigators, that there may be an accelerated decrease with age in cellular immunity in the heavily exposed group (100+ rad) as compared with the 0 rad group.[17] Therefore, at this time, the present findings suggest that there is not enough evidence to show that a radiation effect on the antibody detection frequencies is associated with acceleration of immunologic aging.

Continuation and extension of such basic research on human immunologic function in relation to radiation exposure is needed. Unless such studies are continued, we will be unable to cope adequately with the acute and chronic immunologic disorders in aging A-bomb survivors.

原爆被爆の影響を調査するためには，男性群のデータを解析することが合理的であろう。男性の100rad以上群では，三つの臓器すべてに対して加齢に伴う抗体検出頻度の有意な上昇傾向が認められたが，0 rad群においても肝臓に対しては有意な上昇傾向がみられた。

T細胞依存型免疫能が低い者は低年齢，高年齢者とも，放射線の長期的影響を受けやすいことが動物実験により報告されている。[13-16] ヒトに関しては，全身又は細胞レベルにおいても，この問題を扱う報告はほとんどない。唯一の報告は我々によるもので，高線量被曝群（100rad 以上）においては，0 rad 群と比較すると，加齢に伴う細胞免疫の急激な減少が見られることを示唆するものである。[17] したがって今回得られた所見は，抗体検出頻度に対する放射線の影響が，免疫的な加齢の促進に関連することを示す十分な証拠はないことを示唆している。

ヒトの免疫機能と放射線被曝との関係についてこのような基本的研究を続行し，拡大することは極めて重要である。このような研究が継続されなければ，我々は高齢化する原爆被爆者における急性及び慢性の免疫的障害に適格に対処していくことはできないであろう。

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