TECHNICAL REPORT
23-59
業 績 報 告 書

HEMATOLOGIC STUDIES OF IRRADIATED SURVIVORS IN HIROSHIMA, JAPAN

広島における原爆被爆生存者の血液学的研究

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長崎における原子爆弾被爆生存者に発生した抗療性貧血

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ATOMIC BOMB CASUALTY COMMISSION
ABCC

EDITOR'S NOTE
編集者の言葉

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ATOMIC BOMB CASUALTY COMMISSION
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Refractory anemia was one of the first pathologic effects noted as a result of exposure to radioactive agents. Since the original description, published over forty-five years ago, a number of reports have appeared in the literature describing the occurrence of refractory amemia as a late effect of repeated exposures to x-rays or various radioactive materials.[1,2,3] The susceptibility of the hematopoietic tissues to irradiation is well known and the severe effects on the bone marrow accompanying acute radiation injury have been described by a number of observers.[4,5,6] However, to date refractory anemia has not been described as a late manifestation of radiation injury among survivors of the atomic bombings. The present paper is a report on six cases of refractory anemia occurring in Nagasaki survivors four to seven years after the atomic bombing. Autopsy findings are presented in five of the six cases.

抗療性貧血は放射性物質による照射の結果認められた最初の病理学的影響の一つであった。この疾患のことが45年以上も前に初めて発表されて以来，X線または他の放射性物質に繰返し曝されると，後影響として抗療性貧血の発生をみるという報告が文献に掲載された[1-3]。造血組織が放射線に対して感受性が高いことは周知のことであり，急性放射線傷害に伴って骨髄に重篤な影響があるということが多くの観測者によって報告されている[4-6]。しかしながら，現在まで抗療性貧血が原爆被爆生存者における放射線後障害として報告されたことはない。この報告書は原爆後4～7年経過した長崎被爆生存者6名に発生した抗療性貧血に関する報告である。6症例中5症例について剖検所見も報告されている。

METHODS AND MATERIAL

During the investigation of late radiation effects by the Atomic Bomb Casualty Commission(ABCC), three patients were encountered with symptoms of refractory anemia. Previously, as part of the investigation, autopsies had revealed a refractory anemia in two individuals. Subsequent to the recognition of these cases a survey was made of all of the death certificates in Nagasaki during the years 1949 to 1951 inclusive. One additional case of refractory anemia was discovered.

方法および材料

原爆傷害調査委員会（ＡＢＣＣ）が放射線による後影響を調査中に抗療性貧血の症状を有する3人の患者を発見した。以前調査の一部として行なわれた剖検の結果2例の抗療性貧血が認められた。これらの症例を発見後1949年より1951年に至る間の長崎の死亡診断書の全部について調査を行なった。その結果抗療性貧血1症例を更に発見した。

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原爆傷害調査委員会　臨床検査室

Routine hematologic studies, including bone marrow examinations, were made on the three patients studied at the ABCC clinic. Data on the other three were furnished by their physicians. In addition to the usual clinical and laboratory data, a careful radiation history was recorded. This included the exact location of the individual at the time of the bomb burst and the development of any subsequent radiation symptoms. In this report the exposure distances are recorded in meters from the ground center beneath the bomb explosion.

ＡＢＣＣの診察で発見された３例について骨髄検査を含む一般血液検査を実施した。他の３例に関する資料は夫々の医師から提供を受けた。一般臨床ならびに検査資料のほかに詳細な放射線歴をとった。これには原爆炸裂時の正確な位置およびその後に発生した放射線症状も含められた。本報告中，被爆距離は爆心地点からメートルで記録した。

CASE HISTORIES

症　　歴

Case 1, T C.

T. C., a fifty-one year old Japanese male school teacher, was exposed to the atomic bomb at a distance of 500 meters and subsequently developed an acute radiation syndrome. He remained in a critical condition for months with anemia, hemorrhagic diathesis, and epilation. His hair began to grow back about the third month.

症例１，Ｔ.Ｃ.，日本人男子，51才，教員

500m の距離で被爆し，その後急性放射能症状を呈した。貧血，出血性素質，脱毛で数カ月も重篤な状態が続いた。３カ月目頃から毛髪が再び生え始めた。

The patient never fully regained his health; he had a severe anemia and often complained of malaise and dizziness. His position as the principal of a mission school taxed his strength, and when a "work camp" arrived from the United States in August, 1949, he joined the party and performed hard manual labor. His symptoms became progressively more severe from that time on.

患者は完全に健康を取り戻せなかった。重篤な貧血ならびに屢々全身倦怠および眩暈を訴えた。ミッション・スクールの校長の地位にあったことが彼の体力により負担をかける結果となり，1949年８月にアメリカから奉仕団が到着するに及んで，彼は一行に加わり重肉体労働を行なった。爾来彼の症状は更に重篤の度を加えた。

Early in 1950 he was diagnosed as suffering from anemia, probably due to ankylostomiasis, and he received antihelminthic therapy without benefit. On April 8, 1950 he was admitted to the Ureshino National Hospital, where hematologic studies revealed a red blood count of 960,000 per cu. mm., a leukocyte count of 2,900 and thrombocytopenia. From a bone marrow examination the diagnosis of refractory anemia was made. The patient was given several blood transfusions and liver injections, with very little improvement. On May 5, 1950, following a sudden attack of chills and fever, hematemesis occurred. A generalized hemorrhagic diathesis developed, his condition rapidly became worse, and he died on May 13, 1950.

1950年初期に十二指腸虫症によると思われる貧血に罹患していると診断され，駆虫剤療法を受けたが効果は認められなかった。1950年４月８日国立嬉野病院に入院した。同病院における血液検査の結果，赤血球数960,000(/㎣)，白血球数2,900(/㎣) 及び血小板減少症を認めた。骨髄検査の結果抗療性貧血の診断がなされた。輸血ならびに肝臓注射を数回行なったが殆んど軽快を見なかった。1950年５月５日悪寒と発熱の後に吐血があった。全身性出血素質が発生し，病状は急速に悪化し，1950年５月13日鬼籍に入った。

The autopsy findings were as follows:

剖検所見は次の通りであった。

Gross Findings

There were numerous petechiae scattered over the body and hemorrhages were found in the epicardium, kidneys, base of the brain, and the mucosal surfaces of the stomach and intestinal tract. The spleen measured 11 x 7 x 2.5 cm. and weighed 44 gm.; the capsule was smooth and free of adhesions; the parenchyma appeared hyperplastic. The liver measured 27 x 19 x 6 cm. and weighed 2650 gm.; the capsule was smooth and the parenchyma a pale yellow-brown with a prominent lobular pattern. The remainder of the organs were not remarkable.

Microscopic Findings

Bone marrow. There was a moderately diffuse increase in fat with a delicate reticulum network (fig. 1). There was a marked diminution in hematopoietic cells including both erythroid and myeloid elements. A large percentage of the remaining cells were of the lymphoid series. Erythropoiesis was particularly diminished, with only rare normoblasts being present. A small number of myelocytes and earlier myeloid cells were seen, but more mature granulocytes were very few in number. Megakaryocytes in diminished number were present.

Liver. An extensive fatty change was present which was most marked in the central zones where it progressed to a hyaline necrosis (fig. 2). A few mononuclear cells were present in the portal triads.

Summary. In this case there was a fairly typical fatty marrow almost devoid of hematopoietic activity but leaving a delicate reticulum. All hematopoietic elements were reduced in number, particularly the mature forms and perhaps most conspicuously, the erythroid precursors.

Case 2, F. H.

F. H., a forty year old male pathology technician, was exposed to the atomic bomb at a distance of 1040 meters. The patient was working in a room with a large number of people. He was one of four survivors. He suffered flash burns on the arm and left leg, and one week following he had a temperature of 40 C., which continued for one week. A month after exposure, complete epilation

肉眼的所見

全身に多数の点状出血があり，心外膜，腎臓，脳基底部ならびに胃腸管の粘膜に出血がみられた。脾臓の大きさは11×7×2.5*cm*，重さ44ｇ，脾膜は平滑で癒着はなかった。実質は過形成のように見受けられた。肝臓の大きさは27×19×6 *cm*，重さ2650ｇ，被膜は平滑で，実質は薄黄褐色を呈し著明な小葉紋理を認めた。その他の臓器には著変を認めなかった。

顕微鏡的所見

骨髄：脂肪は中等度に瀰漫性に増加し繊細な細網組織を伴なった。（図１）赤血球系ならびに骨髄系の双方を含む造血細胞に著明な減少があり，残余の細胞の大部分はリンパ系のものであった。赤血球造血は特に減少し，まれな正赤芽球のみ存在していた。少数の骨髄球ならびに初期の骨髄性細胞がみられたが成熟した顆粒球は非常に少数であった。少数の巨核球が存在した。

肝臓：広範囲に及ぶ脂肪性変化は中心部において最も著明に現われ，そこで硝子質壊死にまで進行していた（図２）。小数の単核細胞が肝門部に存在した。

総括：本症例において造血活動は殆んど欠如しながら繊細な細網が残ったかなり典型的な脂肪髄が認められた。すべての造血細胞は減少していた。これは特に成熟細胞において認められたが最も目立っていたと思われるのは前赤血球においてであった。

症例２，Ｆ.Ｈ.　男子，40才，病理技術員

1040ｍの距離で被爆した。本人は多数の人々と同室で働いており，４人の被爆生存者中の１人であった。腕ならびに左脚に閃光による火傷をうけ，１週間後より 40° C の熱が１週間続いた。被爆１カ月後に毛髪が完全に脱落した。既往歴ならびに家族歴には特記すべき事項はなかった。

occurred. The past history and family history were not contributory.

In September, 1951 the patient developed fatigue and abdominal pain, and at that time a diagnosis of peptic ulcer was considered. In November, 1951 he was treated for ankylostomiasis, but during February the abdominal pain increased and was accompanied by diarrhea. At this time x-ray studies revealed a gastric ulcer, and the patient was treated by diet therapy. On May 19, 1952, due to the persistence of complaints, the patient visited the Medical School of Nagasaki University, where a severe anemia and leukopenia were discovered. He was admitted to the hospital.

1951年9月患者は疲労感ならびに腹痛をおこし，消化性潰瘍の診断がなされた。1951年11月患者は十二指腸虫症の治療を受けたが，2月に腹痛が激しくなり同時に下痢を伴った。X線検査の結果胃潰瘍を認めたので患者は食餌療法を受けた。1952年5月19日主訴が持続するので患者は長崎大学医学部を訪れ，そこで重篤な貧血ならびに白血球減少症が発見された。患者は同病院に入院した。

On physical examination, the pulse rate was 80 and the blood pressure 90/40. The patient appeared chronically ill with marked pallor, and he appeared to have lost weight. There were scars of flash burns on the arms and left leg. The superficial cervical lymph nodes were palpable but not enlarged. On auscultation of the chest the breath sounds were distant, and a soft blowing systolic murmur was heard at the cardiac apex. The abdomen was flat and no organs or masses were palpable, but slight epigastric tenderness was present.

全身検査で脈搏80，血圧 $^{90}/_{40}$ であった。患者は慢性疾患の様相があり顔面は著しく苍白であり体重の減少もあったように見受けられた。腕ならびに左脚に閃光による熱傷瘢痕があった。表在性頸リンパ腺は触れたが腫大を認めなかった。胸部聴診では呼吸音はかすかで心尖部に軟らかい吹鳴性収縮期雑音を聴取した。腹部は平滑で臓器も腫瘤も触れなかったが軽度の上腹部圧痛があった。

Hematological findings were as follows. Red blood count was 1,770,000 per cu. mm., hemoglobin 5.7 gm. per cent, reticulocyte count was 0.2 per cent, and the platelets numbered 93,330 per cu. mm. The leukocyte count was 1,800 per cu. mm., with a differential of 2 per cent segmented forms, 16 per cent stab forms, 50 per cent lymphocytes, 28 per cent monocytes, and 4 per cent eosinophils. Bone marrow examination showed 8.5 per cent segmented forms, 7.5 per cent stabs, 11.5 per cent juveniles, 30 per cent myelocytes, 7.5 per cent promyelocytes, 5.0 per cent myeloblasts, 1 per cent polymorphonuclear basophils, 5.5 per cent polymorphonuclear eosinophils, 22.5 per cent lymphocytes and 1 per cent reticulum cells. For 200 leukocytes there were 22 erythroid cells composed of 8 normoblasts, 13 late erythroblasts, and 1 early erythroblast. The megakaryocytes were decreased and the marrow showed definite erythroid hypoplasia.

血液検査所見は次の通りであった。

赤血球数は1,770,000 (/㎣)，血色素量5.7g%，網状赤血球数0.2%，血小板数93,330 (/㎣)，白血球数1,800 (/㎣)，同分類像：分節球2%，杆核球16%，リンパ球50%，単球28%，好酸球4%。骨髄検査の結果，分節球8.5%，杆核球7.5%，幼若型11.5%，骨髄球30%，前骨髄球7.5%，骨髄芽球5.0%，多形核好塩基球1%，多形核好酸球5.5%，リンパ球22.5%，細網細胞1%，白血球200に対し正赤芽球8，後期赤芽球13ならびに前期赤芽球1よりなる赤血球系細胞22があった。巨核球は減少し，骨髄は赤血球形成不全をはっきり示した。

Subsidiary microscopic findings included the presence of pulmonary edema, chronic cystitis and focal hyperspermatogenesis.

Summary. The findings were compatible with a diagnosis of refractory anemia, and there was no organ infiltration to suggest a diagnosis of leukemia.

副次的顕微鏡所見として肺水腫，慢性膀胱炎ならびに限局性過精子形成があった。

総括：所見は抗療性貧血の所見と一致し，白血病の診断を示唆する臓器浸潤はなかった。

Case 3, M. C.

M. C., a twenty-two year old female office clerk, was exposed to the atomic bomb at a distance of 1250 meters. At the time of the explosion she was standing inside a wooden house with about twentyfriends, almost all of whom died within a short while. The patient suffered flash burns on the left side of the face and cut wounds on the right side of the face and right leg. A few days later she noticed a low-grade fever and developed loose stools. A month after the bombing she developed oropharyngeal lesions which lasted five days, and at the same time, swelling and bleeding of the gums occurred. Twenty days after the bombing epilation started and became almost total.

The patient's father, mother and one sister died as a direct result of the bombing; otherwise the family history and past history were noncontributory.

The patient was seen in the Commission's clinic on February 15, 1952 in a routine survey of adult survivors of the atomic bomb. She complained of tiredness and left lateral chest pain. The patient had noted that she developed infections easily since her exposure to the atomic bomb.

Examination at the time of this visit was negative except for the presence of radiation cataracts.

Laboratory Examinations

Hookworm ova were found in the stool specimens, and the guaiac test was positive. The S.T.S. and urine were both negative. The hematology was as follows: red blood count 3,465,000 per cu. mm., hemoglobin 9.4 gm. per cent, hematocrit 32.5 per cent, MCV 99 cu. microns, MCH 27 micromicrograms (γγ), MCHC 29 per cent, reticulocytes 0.5 per cent, Wintrobe sedimentation rate 30.0mm. (1 hr.), platelets 349,965 per cu. mm. The leukocyte count was 4,650 per cu. mm., with a differential of

症例3，M.C．女子，22才，事務員

1250mの距離で被爆，爆発時当人はおよそ20人の友人と一緒に木造家屋内に立っていた。友人のほとんど全員は短期間で死亡した。患者は顔面左側に閃光による火傷を，また顔面右側ならびに右脚に切傷を受けた。数日後に微熱を生じ下痢をした。被爆1カ月後に口腔咽頭部に病変を生じ5日間続いた。同時に歯齦腫脹ならびに出血をみた。被爆20日後に脱毛が始まり殆んど完全な脱毛状態となった。

患者の両親と妹1人は被爆が直接の原因で死亡した。そのほかは家族歴ならびに既往歴には特記事項を認めなかった。

患者は1952年2月15日成人被爆生存者の一般検査のため，当委員会外来において診察を受けた。患者は疲労感と左外側胸痛を訴えた。患者は被爆以来感染症にかかりやすい状態にあることに気付いていた。

この診察では放射性白内障を認めたほかは異常を認めなかった。

臨床検査

検便では十二指腸虫卵を認めた。グアヤク検査は陽性であった。血清梅毒検査ならびに検尿はいずれも陰性であった。血液検査の結果は次の通りであった。赤血球数3,465,000 (/mm³)，ヘモグロビン9.4g%，ヘマトクリット32.5%，平均赤血球容積99立方ミクロン，平均赤血球血色素量27ミクロミクログラム (γγ)，平均赤血球血色素濃度29%，網状赤血球0.5%，ウイントローブ赤血球沈降率30.0mm (1時間)，血小板数349,965 (/mm³)，白血球数4,650 (/mm³)，同分類像は

segmented forms 60.5 per cent, stabs 2.0 per cent, lymphocytes 23.5 per cent, monocytes 1.5 per cent, eosinophils 10.5 per cent, and basophils 2.0 per cent. Slight anisocytosis was seen. The chest x-ray revealed a strand of increased density at the right base but no evidence of active disease.

Subsequent Course

At a local hospital in April, 1952 a provisional diagnosis of pernicious anemia was made and she was treated with Vitamin B_{12} and liver extract. Bone marrow examination revealed granulocytic segmented forms 10.5 per cent, stabs 9.5 per cent, juveniles 11.0 per cent, myelocytes 10.5 per cent, promyelocytes 8.0 per cent, myeloblasts 1.0 per cent, polymorphonuclear basophils 2 per cent, polymorphonuclear eosinophils 1 per cent, lymphocytes—small 38 per cent, reticulum cells 6 per cent, and plasma cells 2.5 per cent. There were 201 nucleated red blood cells per 200 nucleated white blood cells, normoblasts 109, late erythroblasts 75, and early erythroblasts 17. The marrow was hypo cellular with decreased megakaryocytes and increased lymphocytes. No megaloblasts were seen and the hemoglobinization of the erythroid elements was defective.

The patient was seen a second time by Commission physicians on May 23, 1952 and was found to be in extremis. For a month the patient had been bedfast with bleeding gums and persistent bleeding from the vagina. On examination there was extreme pallor, evidence of old hemorrhage about the gums, and active bleeding from the vagina. The pulse rate was 130. There were no enlarged glands and the liver and spleen were not palpable. The tongue, although pale, showed no atrophy of the papillae.

The red blood count was 770,000 per cu. mm. with 2.0 gm. per centhemoglobin and a hematocrit of 7.0. The platelet count was 13,000, white blood count 3,900 per cu. mm. with a differential of 5 per cent segmented forms, 5 per cent stabs, 49 per cent lymphocytes, 3 per cent monocytes, 1 per cent eosinophils, 2 per cent metamyelocytes, 9 per cent myelocytes, 21 per cent promyelocytes, and 5 per cent myeloblasts.

The patient was immediately hospitalized and transfused with 300－400 cc. of blood. Three

分節球60.5%，杆核球2.0%，リンパ球23.5%，単球1.5%，好酸球10.5%，好塩基球2.0%，軽度の不同細胞症が見られた。胸部X線検査の結果，右基底部に糸状の陰影増強を認めたが，活動性疾患の徴候はなかった。

その後の経過

1952年4月に地方の病院で悪性貧血という仮診断がなされ，患者はビタミンB_{12}ならびに肝臓エキスによる治療を受けた。骨髄検査の結果分節球10.5%，杆核球9.5%，幼若型11.0%，骨髄球10.5%，前骨髄球8.0%，骨髄芽球1.0%，多形核好塩基球2%，多形核好酸球1%，リンパ球（小）38%，細網細胞6%，形質球2.5%，有核白血球200につき有核赤血球201あった。正赤芽球109，後期赤芽球75，初期赤芽球17，骨髄には細胞が減少し，巨核球の減少ならびにリンパ球の増加を認めた。巨大赤芽球は見られず赤血球系のヘモグロビン含有は不良であった。

患者は1952年5月23日当委員会医師により第2回診察を受けたが末期的状態にあった。歯齦出血ならびに持続性の膣出血で患者は1カ月間床についていた。診察時強度の蒼白があり歯齦附近に古い出血ならびに活動性の膣出血の徴候があった。脈搏130，肥大した腺はなく肝臓並びに脾臓を触れなかった。舌は淡色であったが乳頭の萎縮を認めなかった。

赤血球数770,000 (/mm³)，ヘモグロビン2.0g%，ヘマトクリット7.0。血小板数13,000，白血球数3,900 (/mm³)，同分類像：分節球5%，杆核球5%，リンパ球49%，単球3%，好酸球1%，後骨髄球2%，骨髄球9%，前骨髄球21%，骨髄芽球5%。

患者は直ちに入院のうえ300～400cc の輸血を受けた。胸骨並びに腸骨稜から骨髄液を採取すべく3回行

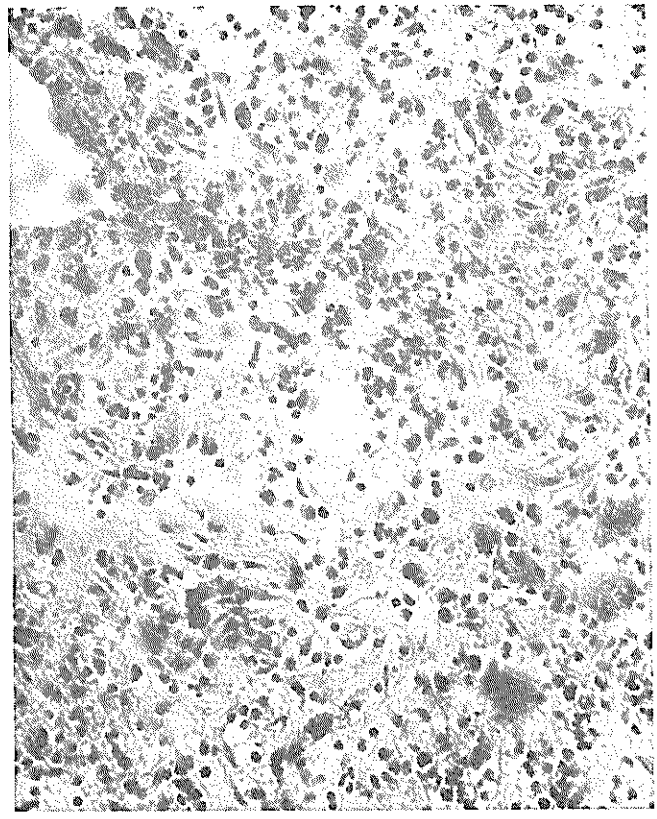

Fig. 3.—Bone marrow from sternum of case 3 showing extensive fibrosis (×400).
図　3　広範囲に亘る線維症がみられる症例3の胸骨骨髄（×400）

unsuccessful attempts were made to aspirate marrow from the sternum and iliac crest. She expired on May 26, 1952, seventy-two hours after admission. Eighteen hours after death an abdominal incision was made and specimens were obtained from the liver, spleen and right kidney. A section of the sternum for bone marrow examination was taken.

なったが不成功に終った。患者は入院72時間後の1952年5月26日に死亡した。死亡18時間後に腹部切開を施行し，肝，脾臓ならびに右腎から標本を採取した。骨髄検査のため胸骨の一部を採取した。

Pathohistologic Findings

Bone marrow. There was a diffuse and extensive fibrosis involving the entire marrow space of the available section (fig. 3). Enmeshed singly or in small clumps throughout the fibrous tissue were greatly diminished numbers of hematopoietic cells. Among these it was noted that there was a relative diminution of early myeloid forms, with only a few myelocytes and occasional nonsegmented leukocytes present in proportion to the segmented forms. The erythroid elements were more conspicuously those of the erythroblastic level; normoblasts were few in number. Megakaryocytes were

病理学的所見

骨髄：瀰漫性かつ広範囲に亘る線維形成が胸骨切片の全骨髄間隙にみられた（図3）。非常に数の減少した造血細胞が線維組織のいたるところに単独もしくは小塊で存在していた。この中に初期骨髄系は比較的に減少しており，分節球に比べて少数の骨髄球と非分節白血球が存在していることを認めた。赤血球系には赤芽球の段階のものが目立って多く正赤芽球は少数であった。

present but were for the most part smudged or bizarre. A large proportion of the cells present were lymphocytes and plasma cells.

巨核球は存在したが多くは不鮮明で変形していた。細胞の大部分はリンパ球ならびに形質球であった。

Spleen. The capsule was very slightly thickened, and the lymphoid germinal centers were small with congested sinusoids. Moderate quantities of hemosiderin were present, and the red pulp was diffusely infiltrated by a great variety of cells, including large and small lymphocytes. Erythroblasts, normoblasts, and a few myelocytes could be distinguished and a number of degenerating megakaryocytes were present.

脾臓：被膜は極めて軽度に肥厚し，リンパ胚中枢は小さく鬱血性の洞様構造であった。中等量のヘモシデリンが存在し大小のリンパ球を含むいろいろの細胞が赤色髄に瀰漫性に浸潤していた。赤芽球，正赤芽球ならびに少数の骨髄球を識別することが出来，若干の退行性巨核球が存在していた。

Liver. There was moderate congestion of the central portions of the liver lobules, with fatty degeneration and foci of early hyaline necrosis in these areas. The periportal connective tissue was moderate in amount and was diffusely infiltrated with small round cells, mostly lymphocytes. The sinusoids contained small islands of round cells with dark nuclei and a slightly basophilic cytoplasm resembling that of erythroblasts and normoblasts. Occasional hypersegmented or degenerating neutrophilic leukocytes were seen, together with a few large cells with degenerating nuclear masses which probably represented megakaryocytes.

肝臓：肝小葉の中心部に中等度の鬱血があり脂肪変性ならびに早期硝子質壊死の病巣があった。門部周囲の結合組織の量は中等度であり主としてリンパ球から成る小型円形細胞が瀰漫性に浸潤していた。洞様構造は暗色核を有する円形細胞の小さい島ならびに赤芽球および正赤芽球に類似したやや好塩基性の細胞形質を含んでいた。巨核球に相当すると思われる変性核集団を有する少数の大型細胞と共に所々に過分節型ないし変性好中性白血球がみられた。

Summary. The single marrow section studied was compatible with refractory anemia in which the marrow cavity showed extensive fibrosis. In this case hematopoietic cells persisted in the fibrous tissue. This picture could not be differentiated from that seen in refractory anemia due to other toxic agents. Extramedullary hematopoiesis, particularly erythropoiesis, was present in the spleen and liver.

総括：検査された1個の骨髄切片が抗療性貧血と一致し，骨髄腔は広範囲に亘る線維症を示した。本症例において造血細胞が線維組織内に残っていた。この像はその他の毒性作用に基因する抗療性貧血にみられるものと区別することができなかった。骨髄外造血特に赤血球造血は脾臓ならびに肝臓に認められた。

Case 4, K. K.

This fifty-one year old farmer was exposed to the atomic bomb at a distance of 1500 meters. He received injuries to the left parietal region and subsequently developed some of the symptoms of the acute radiation syndrome, namely, vomiting, fever, diarrhea and epilation. Apparently the patient recovered fairly completely, but he continued to complain of general weakness.

The past history was not contributory.

症例4，K.K.　男子，51才，農夫

1500mの距離で被爆し，左頭頂部に傷を受けその後嘔吐；熱，下痢ならびに脱毛などの急性放射線症状が現われた。外見上，患者はほぼ完全に回復したが，全身性衰弱の訴えが続いた。

既往歴には特記事項を認めなかった。

In September, 1951 the patient developed furunculosis of the right cheek and he noted pain and bleeding of the gingivae. The left side of his face became edematous and his temperature was elevated to 39 C. Palpitation and dizziness on exertion also developed at this time.

He was seen at the clinic of the ABCC on 24 October 1951. Physical examination revealed an extremely pale and acutely ill Japanese male. The temperature was 38.2 C.; pulse, 90; and blood pressure, 110/58. Small bilateral cervical nodes and small axillary nodes were noted. The examination of the fundi revealed old and new hemorrhages, some of them flame-shaped. The heart was slightly enlarged to percussion and a soft systolic murmur was heard over the precordium. The liver was questionably palpable one finger breadth below the costal margin. The spleen was not palpable.

Laboratory Data

Hematology. Red blood count was 690,000 per cu. mm. with a hemoglobin of 2.0 gm. per cent. White blood count was 5,000 per cu. mm. with a differential of 23.5 per cent segmented forms, 4.5 per cent stabs, 55 per cent lymphocytes, 11.5 per cent monocytes, 1 per cent eosinophils, 2.5 per cent basophils, 1 per cent metamyelocytes, 1 per cent myelocytes. One normoblast was seen and the platelets were markedly reduced in number.

Sternal marrow aspiration was carried out and grossly normal clumps of marrow were obtained. On microscopic examination, some areas of active cellularity were present. Erythroid elements were markedly decreased, and there was a decrease in myeloid activity with a slight shift to immaturity. There was an increase in mononuclear cells, eosinophils, plasma cells, reticulum cells and mast cells.

On the basis of these findings, a diagnosis of refractory anemia was made, and the patient was advised to enter the hospital immediately.

During the hospital course the hematological values of erythroid elements remained unchanged. The white blood count fell to 2,800 per cu. mm. In spite of therapy with iron, penicillin and blood transfusions, the patient expired on November 2, 1951, ten days after admission.

1951年9月右頬に癰腫が現われ，歯齦に疼痛ならびに出血があった。顔面左側が浮腫状を呈し体温39°Cに上昇した。労作時に動悸ならびに眩暈もまたこの時現われた。

患者は1951年10月24日ＡＢＣＣ外来で診察を受けた。全身検査では極度の蒼白ならびに急性疾患のあることを認めた。体温38.2°C，脈搏90，血圧110/58。両側頸部ならびに腋窩に小結節を認めた。眼底検査では新旧の出血を認めそのうち火焔型のものもあった。打診で心臓は軽度に肥大し，前胸部に軟かい収縮期雑音を聴取した。肝臓は肋弓下一横指に触れたようであった。脾臓は触れなかった。

臨床検査所見

血液検査：赤血球数690,000 (/㎣)，ヘモグロビン2.0g%，白血球数5,000 (/㎣)，同分類像：分節球23.5%，杆核球4.5%，リンパ球55%，単球11.5%，好酸球1%，好塩基球2.5%，後骨髄球1%，骨髄球1%，正赤芽球1個を認め血小板は著明に減少していた。

胸骨骨髄採取の結果肉眼的に正常な骨髄塊を得た。顕微鏡検査では若干の活動性細胞充実領域があった。赤血球系は著明に減少し，骨髄活動は減少し，軽度の幼若傾向があった。単核細胞，好酸球，形質球，細網細胞ならびに肥胖細胞は増加していた。

以上の所見に基づいて抗療性貧血の診断がなされ，直ちに入院するよう勧告がなされた。

入院中赤血球系の血液学的数値は変らなかった。白血球数は2,800 (/㎣) に減少した。鉄，ペニシリンならびに輸血による加療も空しく患者は入院後10日目の1951年11月2日死亡した。

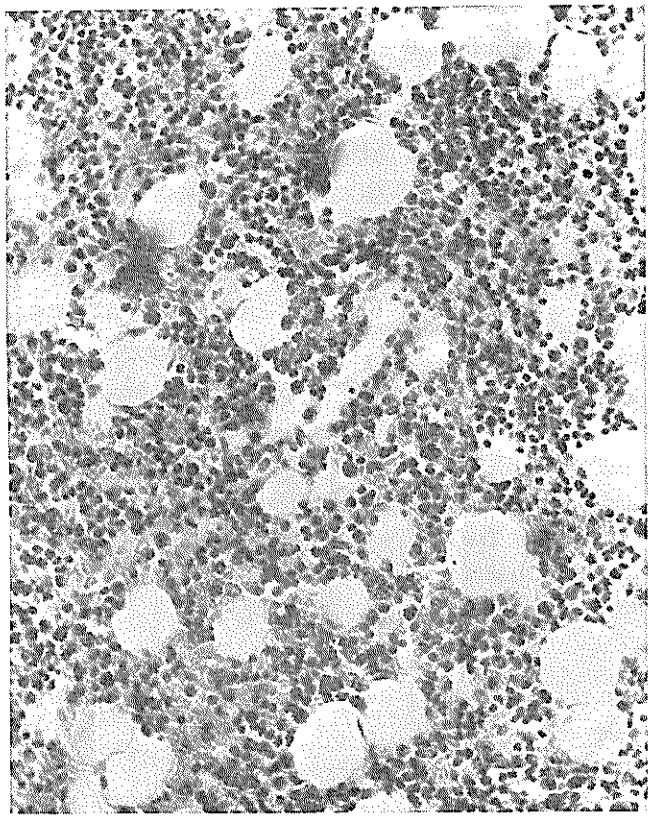

Fig. 4.—Bone marrow of case 4 showing a cellular portion of the marrow in this case (×400).
図　4　症例4の骨髄の細胞に富む部分（×400）

Autopsy Findings

Extreme pallor of mucous membranes and organs, as well as numerous petechiae were noted. Several small mesenteric lymph nodes varying in size up to the size of a pea were found, which, on cross section, were yellowish-white in color. The spleen weighed 45 gm., it was firm in consistency with normal elasticity, and the capsule was tense. The liver weighed 940 gm., was firm in consistency, and showed no other abnormality.

剖検所見

多数の点状出血と共に粘膜ならびに臓器は極度に蒼白であった。豌豆大にまで及ぶ色々の大きさの小腸間膜リンパ腺数個が発見され，断面は黄白色を呈した。脾臓は重さ45ｇ，硬く正常な弾力性があり被膜は緊張性があった。肝臓は重さ940ｇ，硬くその他の異常を認めなかった。

Microscopic Findings

Bone marrow. Two sections of marrow were available. In each there were large areas of hemorrhage and replacement of marrow cells by fat. Elsewhere there was active hematopoiesis with the marrow appearing hyperplastic in some zones (fig.4.). The marrow appeared definitely abnormal in that there was a lack of myeloid maturation with relatively few segmented forms being seen. Large numbers of eosinophilic elements were present.

顕微鏡的所見

骨髄：２個の標本が検査のため入手できた。

各標本においては広範に亘って出血があり，骨髄細胞は脂肪によって置き換えられていた。ほかの場所には活動性造血があり，ある部分において過形成の様相がみられた（図４）。骨髄には骨髄球熟成の欠如と相対的に少数の分節球があり明らかに異常があるようにみえた。多数の好酸性球が存在していた。赤血球系細

The erythroid cells were relatively and absolutely reduced, and megakaryocytes were very few in number. Lymphocytes were increased and pigment was abundant.

Spleen. There was marked hemosiderosis.

Liver. There was subcapsular atrophy and extreme central congestion with areas of hyaline necrosis. In the extremely congested central sinusoids there were numerous white blood cells, some of them identified as myelocytes, but erythroid elements could not be definitely discerned. In the periportal connective tissue there were small foci of lymphocytic infiltration.

Summary. The marrow had several features unlike those of the other cases in this series. Those areas that were hemorrhagic appeared to have been largely replaced by fat. Elsewhere the marrow had a pseudohyperplastic appearance, but on closer study proved to contain many lymphocytes and plasma cells with a striking diminution in erythropoiesis and an almost complete absence of megakaryocytes.

Case 5, M. S.

M. S., a seventy-one year old Japanese male school supplier, was exposed to the atomic bomb at 3800 meters. He had no radiation symptoms following the bombing.

The patient began to notice mild fatigability in 1948. In September, 1951 he developed a fever and noticed the presence of petechiae on his arms and chest, and later these extended to cover his entire body.

It is of interest that at about this same time he started supplying various inorganic chemical compounds to schools. These compounds included hydrochloric acid, sulphuric acid, nitric acid, potassium hydroxide, sodium hydroxide, ammonia, zinc, magnesium, sulphur and other ores. He obtained bulk materials from the pharmacists and packed and labeled the containers in his shop. This was his only known contact with chemical substances, none of which is known to be implicated in causing refractory anemia.

His blood counts at this time were as follows: red blood cells, 1,000,000 per cu. mm.; white blood cells 1400 per cu. mm., with a differential showing 26 per cent segmented forms, 2 per cent eosinophils,

胞数の相対値もその絶対値も減少し巨核球は極めて少数しかなかった。リンパ球は増加し，色素は豊富であった。

脾臓：著明なヘモシデリン沈着症があった。

肝臓：硝子質壊死部を伴う被膜下出血ならびに中心部に極度の鬱血があった。極度に鬱血した中心部洞様構造において多数の白血球があり，そのあるものは骨髄球と識別し得たが，赤血球系は明確に識別し得なかった。門部周囲の結合組織にリンパ球浸潤の小病巣があった。

総括：骨髄は本調査における他の症例が持っていた特徴と異るいくつかの特徴を有していた。出血性であった部位の大部分は脂肪により置き換えられているようであった。その他の場所で骨髄は偽過形成の外観を呈したがより詳細な調査の結果，多数のリンパ球ならびに形質球を含んでいることが判明し，顕著な赤血球生成の減少と巨核球の殆んど完全な欠如とを認めた。

症例5，M．S．　日本人男子，71才，学校教材取扱店主

3800mで被爆したがその後放射線症状はなかった。

1948年に軽い疲労を感じ始めた。1951年9月発熱し腕および胸部に点状出血を認めその後全身をおおうまで拡がった。

これとほぼ時を同じうして当人は種々の無機化合物を学校に供給する仕事を始めたことは興味あることである。これらの化合物には塩酸，硫酸，硝酸，水酸化カリウム，水酸化ナトリウム，アンモニア，亜鉛，マグネシウム，硫黄ならびにその他の鉱物があった。薬剤師から大量に材料を購入して自分の店で容器に詰めレッテルを貼っていた。彼が化学薬品と接触を持ったのはこの一度だけであって，その中で抗療性貧血の原因となる物質はなかった。

この当時の血球数は次の通りであった。

赤血球数1,000,000(/㎣)，白血球数1,400(/㎣)，同分類像：分節球26%，好酸球2%，リンパ球70%，単球2%。

70 per cent lymphocytes, and 2 per cent monocytes.

The patient was treated with Vitamin B_{12}, reduced iron and blood transfusions. Chloromycetin, penicillin and a sulfonamide preparation were also used in an effort to control the fever. (There was no history of the patient's receiving Chloromycetin before the development of the anemia.) The patient died on October 9, 1951. Permission for autopsy was not granted.

患者にビタミンB_{12}，還元鉄，ならびに輸血を行なった。熱を抑えるためにクロロマイセチン，ペニシリンならびにサルファ剤を使用した。（貧血の発生前患者がクロロマイセチンによる治療を受けたことはなかった)。患者は1951年10月9日に死亡した。剖検の許可は得られなかった。

Case 6, I. Y.

This fifty-six year old Japanese male accountant was exposed to the atomic bomb at a distance of 4,400 meters. On the day following the bombing, he walked through the area directly beneath the bomb burst and spent a considerable period of time in the ruins of a steel factory nearby. However, he did not have any symptoms of the acute radiation syndrome.

症例6，I.Y. 日本人男子，56才，計理士

4400mの距離で被爆，原爆投下の翌日爆心地を歩き近くの鋼鉄工場の廃墟のなかでかなり長時間過した。しかしながら，急性放射線症候群の症状はなかった。

The family history is of interest in that one of his sons died of leukemia in 1947, but this boy was not exposed to the atomic bomb.

息子の1人が1947年に白血病で死亡したがこの少年は原爆に被爆しなかったという点はその家族歴で興味あることである。

The patient was apparently well until 1948, when he began to complain of general lassitude, palpitation on exertion, and edema of the lower extremities. In April, 1951 a swelling of the left side of the face was noted, as well as a more marked sense of fatigue and a gradual weight loss. On the 9th of September, 1951 the patient first noted tinnitus, slight deafness, and vertigo. He entered the hospital of the Nagasaki Medical School on September 10, 1951.

患者は1948年まで外見上は健康であったがその時期に全身倦怠，労作時動悸ならびに下肢の浮腫を訴え初めた。1951年4月顔面左側の腫脹を認め疲労感は一層顕著となり体重は次第に減少した。1951年9月9日患者は初めて耳鳴り，軽微の難聴ならびにめまいに気付いた。1951年9月10日患者は長崎大学医学部付属病院に入院した。

On physical examination, the blood pressure was 90/45. The patient was slightly emaciated and a noticeable pallor was present. The heart was slightly enlarged to the left and a systolic murmur was heard over the precordium. There was no enlargement of the lymph nodes, spleen or liver. The remainder of the examination was not remarkable.

診察時所見。血圧 90/45，患者はやや痩衰し，顕著な蒼白があった。心臓は左に軽度に肥大し，前胸部に収縮期雑音を聴取した。リンパ腺，脾臓および肝臓の肥大はなかった。その他には診察上著変を認めなかった。

Laboratory Findings

The red blood count was 870,000 per cu. mm.; hemoglobin equalled 17 per cent; the leukocyte count was 1,300 per cu. mm. with a differential showing 76.5 per cent lymphocytes. The platelet count was 22,760 per cu. mm.; the bleeding time was twenty minutes, and the congulation time

臨床検査所見

赤血球数870,000 (/mm^3)，ヘモグロビン17%，白血球数1,300 (/mm^3)，同分類像はリンパ球76.5%を認めた。血小板数 22,760 (/mm^3)，出血時間20分，凝固時間6.5分，尿ならびに骨髄液検査は陰性，検便の結果蛔虫卵ならびに十二指腸虫卵を認めた。

six and one-half minutes. Urine and spinal fluid examinations were negative. Stool examinations revealed the ova of ascaris and Ankylostoma.

The patient went rapidly downhill and expired on September 15, five days after entering the hospital. A bone marrow examination performed shortly after death showed the following : 7.4 per cent erythroid elements, 69.6 per cent lymphocytes, 0.6 per cent monocytes, 0.4 per cent promyelocytes, 3.2 per cent myelocytes, 5.2 per cent metamyelocytes, 5.0 per cent stab forms, and 9.4 per cent granulocytic segmented forms.

患者の健康は急速に悪化し，入院5日後の9月15日に死亡した。死亡後間もなく行った骨髄検査の結果次の事項を認めた。赤血球系7.4%，リンパ球69.6%，単球0.6%，前骨髄球0.4%，骨髄球3.2%，後骨髄球5.2%，杆核球5.0%，顆粒球系分節球9.4%。

Autopsy Findings

剖検所見

Gross Findings

肉眼的所見

There was marked pallor of the mucosal surfaces and organs. Areas of hemorrhage were found throughout the intestinal tract. The lymph nodes were not enlarged. The spleen weighed 100 grams, was brownish in color and showed slight congestion. In cross section, the pattern of the trabeculae was not remarkable, but the follicular pattern was obscure. The liver weighed 1250 grams. The bone marrow of the femur was fatty and the sternal marrow appeared pale.

粘膜表面ならびに臓器の蒼白著明，腸管全体に亘り出血を認めた。リンパ腺は腫大せず，脾臓は重さ100gで褐色，軽度の鬱血を認めた。断面では柱像に著変を認めなかったが，沪胞像は不鮮明であった。肝臓は重さ1250g，大腿骨骨髄は脂肪性であって胸骨骨髄は淡色を呈した。

Microscopic Findings

顕微鏡的所見

Bone marrow. The hematopoietic cells were largely replaced by fat, and the remaining cells were for the most part lymphocytes, plasma cells, and reticulum cells (fig. 5). There were scanty focal areas of cellular activity. There were small islands of complete erythroid maturation, but only scattered myeloid forms, mostly of late stages, were present. Megakaryocytes were absent.

骨髄：造血細胞の大部分は脂肪によって置き換えられ，残っている細胞の殆んど大部分はリンパ球，形質細胞並びに細網細胞であった（図5）。細胞活動を有するわずかな限局部があった。完全な成熟赤血球からなる小島があったが，後期に近い形態を有する骨髄球がわずかに散在していた。巨核球は存在しなかった。

Summary. The fatty replacement in this marrow was not so diffuse as that in Case 1. However, in large focal areas, there was practically complete fatty infiltration. It was not clear whether the remaining blood-forming cells represented residual islands of hematopoiesis or isolated foci of regeneration. The absence of megakaryocytes was striking.

総括：この症例における骨髄と脂肪の置換は症例1のそれと比較してそれ程瀰漫性ではなかった。しかしながら広範な限局部において殆んど完全な脂肪性浸潤があった。残存の血液形成細胞が造血の島であるか，孤立した再生部に相当するかは明らかではなかった。巨核球の欠如が目立った。

DISCUSSION

考　　按

All of the cases in this paper conform to a diagnosis of "refractory" hypoplastic anemia

本論文における全症例は"抗療性"低形成性貧血の診断と一致し，貧血，白血球減少症，血小板減少症と

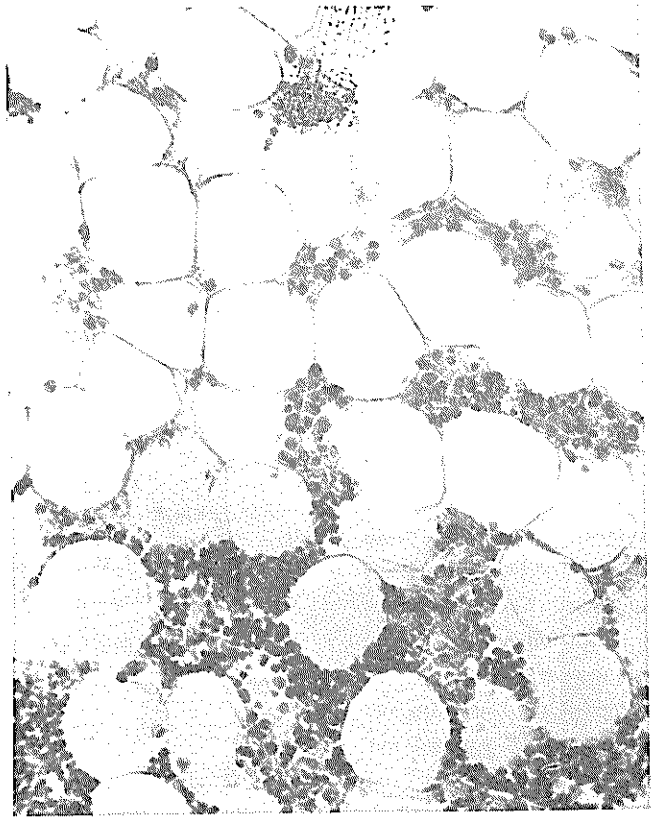

Fig. 5.—Bone marrow of case 6 showing the markedly aplastic marrow with diffuse fatty infiltration. A few islands of hematopoietic tissue remain. (×400).

図　5　瀰漫性脂肪性浸潤を伴う著明に形成不全性骨髄を示す症例6の骨髄。少数の造血組織の島が残る。（×400）

presenting the classical triad of anemia, leukopenia and thrombocytopenia, without significant organ enlargement. Moreover, bone marrow examinations failed to reveal the presence of leukemia and in no case was there evidence of a hypersplenic syndrome. In five cases the diagnosis was confirmed at autopsy. In the sixth case the information was meager, and this patient was not personally studied by the authors. However, this case was included, since all the evidence indicated that the diagnosis of refractory anemia was correct.

It is well known that refractory anemia may present a very variable bone marrow picture.[7] The bone marrows in this series varied from normal cellularity to almost complete aplasia, and in one case to fibrosis. In this case, in addition to myelofibrosis, extramedullary hematopoiesis was present. The different bone marrow pictures represented in this series are shown in the accompanying illustrations.

いう典型的3徴候を示し顕著な臓器腫大はなかった。さらに骨髄検査の結果白血病ではなく，どの症例にも脾機能亢進症候群の徴候はなかった。5症例においては診断は剖検によって確認された。後の1症例は資料が不十分であった。この症例は著者らによって患者の調査がなされなかったが，抗療性貧血の診断が正確であることがあらゆる裏付けにより示されたので本症例を加えた。

抗療性貧血が非常に可変性の骨髄像を示すかも知れないということは十分知られている[7]。本調査例において骨髄は正常な細胞充実性から殆んど完全な形成不全へという変化があり，さらに1症例において線維症があった。この症例においては骨髄性線維症を加えて骨髄外造血があった。本調査に述べられる異った骨髄像は本文中の写真に示した。

Four of the patients were exposed to the atomic bomb explosion at distances of less than 1500 meters, and all four developed definite radiation symptoms. It can be assumed that these patients received a significant insult to their hematopoietic system from atomic radiation. Moreover, it is known that the highest incidence of leukemia has occurred in those survivors who were within a radius of 1500 meters.[8] In all there were 5075 known survivors at distances under 1500 meters from the ground center of the atomic bomb explosion in Nagasaki. Unfortunately there are no accurate statistics on the incidence of aplastic anemia among the general population of either Japan or the United States. However, in clinical experience aplastic anemia is a rare disease, seen even less frequently than leukemia. In view of this fact, the occurrence of four cases of refractory anemia in a population of 5075 individuals representing the survivors under 1500 meters in Nagasaki is suggestive of a probable cause and effect relationship between the exposure to the atomic bomb and the subsequent development of refractory anemia. However, such a relationship is by no means conclusively demonstrated. In the other two individuals exposed beyond 3800 meters, the distance and lack of symptoms of the acute radiation syndrome make it improbable but not impossible that radiation **per se** was a factor in the subsequent occurrence of refractory anemia in their cases.

It is of interest that five similar cases of refractory anemia have been studied in Hiroshima, Japan. These cases will be subsequently reported, together with a survey of the hematopoietic problems arising from late radiation effects.

It is well established that one of the outstanding features of the acute radiation injury occurring in heavily irradiated survivors of the atomic bombing was the rapid occurrence of severe hematopoietic damage.[4,5,6] This damage ranged from complete hypoplasia to minor degrees of bone marrow depression. Similar findings have been reported in animals exposed to radiation under experimental conditions.[9,10] Moreover, there are a number of recorded cases of refractory anemia among early radiologists and other individuals exposed to unshielded radiation over a long period of time.[1,2,3]

患者のうち4名は1500m以内の距離で被爆し各々に明らかな放射線症状が現われていた。これらの患者は造血系に原子放射線による有意の傷害を受けたと考えることができる。さらに1500mの範囲内にあった被爆生存者に最も高い白血病発生率をみたということも知られている[8]。長崎では爆心地から1500m以内の既知の被爆生存者は全部で5,075名であった。不幸にして日本又は米国における一般人口集団についての再生不良性貧血発生率にかんする正確な統計はない。しかしながら，臨床的には，再生不良性貧血は珍らしい疾患であり，白血病より更にまれにしかみられない。この事実に鑑みて長崎における1500m以下の被爆生存者に該当する5,075名からなる人口集団における抗療性貧血4症例の発生は原子爆弾被爆とその後発生した抗療性貧血の間に因果関係のあることを示唆する。しかしながらかかる関係は決して最終的に証明されているわけではない。3800m以上で被爆した他の2名においてはその被爆距離ならびに急性放射線症候群の症状を呈さなかったことから放射線それ自体が抗療性貧血発生の要因であるとは考えられないが全く無視することは出来ない。

同様な抗療性貧血5症例が広島においても研究されたということは興味がある。これらの症例は放射線後影響から生ずる造血問題の調査と共に後で報告されると思う。

原子爆弾による強度の照射を受けた被爆者に発生する急性放射線障害の顕著な特徴の一つは重篤な造血障害が急速に起きたことである[4-6]。この造血障害は完全な形成不全から軽度の骨髄機能低下におよぶ。同様の所見が放射線照射による動物実験において報告されている[9,10]。さらに初期の放射線専門医ならびに無遮蔽で長時間放射線を受けたその他の人々の間に抗療性貧血の症例が認められたとの記録がかなりある[1-3]。

The unusual features of the cases reported in this paper are (1) the radiation insult was due to a single exposure to ionizing radiation, and (2) the fatal hematopoietic damage developed after a latent period of four to seven years without exposure to other known bone marrow toxic agents. The pathogenesis of this disorder remains an enigma, but it is interesting to note that leukemia developing among survivors of the atomic bombing occurs under similar circumstances and after a similar latent period.[8] Since refractory anemia is a much rarer condition, far fewer cases have been found in contrast to the more common leukemia. Further, some studies have shown that erythropoietic tissue is more resistant to radiation than myelopoietic tissue.[11] This has not been universally accepted since other investigators have found the erythropoietic tissues to be quite sensitive to ionizing radiation.[12]

Due to the fact that radioactive isotopes might have been deposited in the bone marrow after exposure to the ionizing effect of atomic energy, the bones of three individuals in this report were analyzed for the presence of any remaining radioactivity. Completely negative results were obtained. This is not conclusive, however, since these studies were made seven years after exposure.

SUMMARY

In this paper the case histories of six Nagasaki atomic bomb survivors who developed refractory anemia are presented. Four of these individuals received undoubted radiation injury. The fact that refractory anemia may occur as a late manifestation of exposure to atomic radiation is pointed out.

本論文において報告された症例の異例な特徴は，(1)放射線傷害が１回限りの電離放射線を受けたことに基因したこと。および(2)致命的造血障害が４～７年の潜伏期間の後に発生し，その間他の既知の骨髄毒素剤にさらされていないこと。本疾患の病因は未だなぞにつつまれているが，原爆被爆者の間に発生する白血病が同様な状況の下で同様な潜伏期間後に発生するということに注目することは興味あることである[8]。抗療性貧血は非常に珍らしい疾患であるからより一般的な白血病と異なりはるかに少数の症例しか発見されなかった。さらにこれまでの調査では赤血球造血組織が骨髄造血組織より放射線により抵抗力があることを示している[11]。また他の研究者は赤血球造血組織が電離放射線に極めて敏感であることを発見したが，これは全般的に認められていない[12]。

原子エネルギーの電離放射線の影響を受けた後に骨髄に放射性同位元素が蓄積せられたかもしれないという事実に基づき，残留放射能の存在を調べるため本報告中の３症例の骨の分析を行なった。完全に否定的結果が得られた。しかしながらこれは被爆７年後に行なわれたものであるから確定的なものではない。

総　　括

抗療性貧血の発病をみた６名の長崎原子爆弾被爆生存者の症例歴を本研究論文に呈示した。このうち４名は明らかに放射線傷害をうけた。原子放射線の照射による後障害として抗療性貧血が発生するかも知れないという事実を指摘する。

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