4. Discussion of:
   a. Establishment of an additional "satellite field office" in Florida; and
   b. Monetary Award for Senior Executive Service Personnel.

FOR MORE INFORMATION CONTACT: Bea Hardesty, (202) 382–6525.

Bea Hardesty,

Federal Register Liaison Officer.

September 2, 1988.

[FR Doc. 88–20430 Filed 9–2–88; 5:01 pm]

BILLING CODE 7533–01–M

OVERSEAS PRIVATE INVESTMENT CORPORATION

MEETING OF THE BOARD OF DIRECTORS

TIME AND DATE: 1:30 p.m. (closed portion), 3:00 p.m. (open portion), Tuesday, September 20, 1988.

PLACE: Offices of the Corporation, fourth floor Board Room, 1615 M Street NW., Washington, DC.

STATUS: The first part of the meeting from 1:30 p.m. to 3:00 p.m. will be closed to the public. The open portion of the meeting will commence at 3:00 p.m. (approximately).

MATTERS TO BE CONSIDERED (Closed to the public 1:30 p.m. to 3:00 p.m.):

1. Finance Project in Oceanian Country
2. Finance Project in West African Country
3. Finance Project in South American Country
4. Finance and Insurance Project in South American Country
5. Insurance Project in South American Country
6. Claims Report
7. Legislative Update
8. Finance Report
9. Finance and Insurance Reports

FURTHER MATTERS TO BE CONSIDERED (Open to the Public 3:00 p.m.):

1. Approval of the Minutes of the Previous Board Meeting
2. Approval of Proposed Regular Meetings of the Board
3. Treasurer's Report
4. Information Reports

CONTACT PERSON FOR INFORMATION: Information with regard to the meeting may be obtained from the Secretary of the Corporation, on (202) 457–7079.

Margaret A. Kole,

OPIC Corporate Secretary.

September 6, 1988.

[FR Doc. 88–20478 Filed 9–6–88; 11:08 am]

BILLING CODE 3210–01–M

TENNESSEE VALLEY AUTHORITY

"FEDERAL REGISTER" CITATION OF PREVIOUS ANNOUNCEMENT: To be published September 6, 1988.

PREVIOUSLY ANNOUNCED TIME AND DATE OF MEETING: 10 a.m. (c.d.t.) Wednesday, September 7, 1988.

PREVIOUSLY ANNOUNCED PLACE AND DATE OF MEETING: Itawamba Community College, Technical Building, Lecture Demonstration Room, 653 Eason Boulevard, Tupelo, Mississippi.

CHANGES IN THE MEETING:

Each member of the TVA Board of Directors has approved the addition of the following item to the previously announced agenda:

B—Purchase awards
   2. Requisition 67—Long Term Spot Coal for Paradise Steam Plant.

CONTACT PERSON FOR MORE INFORMATION: Alan Carmichael, Manager, Public Affairs, or a member of his staff can respond to requests for information about this meeting. Call 615–632–8000, Knoxville, Tennessee. Information is also available at TVA's Washington Office, 202–245–0101.

Edward S. Christenbury,

General Counsel and Secretary to the Board.

[FR Doc. 88–20455 Filed 9–6–88; 11:08 am]

BILLING CODE 8120–01–M

FEDERAL MINE SAFETY AND HEALTH REVIEW COMMISSION

TIME AND DATE: 10:00 a.m., Thursday, September 8, 1988.

PLACE: Room 600, 1730 K Street, NW., Washington, DC.

STATUS: Open.

MATTERS TO BE CONSIDERED: The Commission will consider and act upon the following:

1. *Western Fuels-Utah,* Docket Nos. WEST 86–113–R, etc. (Issues include whether the Administrative Law Judge erred in concluding that Western Fuels violated section 115(a) of the Mine Act and 30 C.F.R. § 48.7 by failing to "task train" a section foreman on a roof bolting machine before his operation on that machine.)
2. *Kaiser Coal Corporation,* Docket No. WEST 88–131–R. (Issues include whether the Commission has jurisdiction to entertain a request for declaratory relief independent of an enforcement action and whether the Administrative Law Judge erred in denying Kaiser's application for declaratory relief.)

Any person intending to attend this meeting who requires special accessibility features and/or auxiliary aids, such as sign language interpreters, must inform the Commission in advance of those needs. Subject to 29 CFR § 2706.150(a)(3) and § 2706.160(d).

CONTACT PERSON FOR MORE INFORMATION: Jean Ellen (202) 653–5629/ (202) 566–2673 for TDD Relay.

Jean H. Ellen,

Agenda Clerk.

[FR Doc. 88–20518 Filed 9–6–88; 4:58 pm]

BILLING CODE 6735–01–M

Corrections

Federal Register
Vol. 53, No. 174
Thursday, September 8, 1988

This section of the FEDERAL REGISTER contains editorial corrections of previously published Presidential, Rule, Proposed Rule, and Notice documents and volumes of the Code of Federal Regulations. These corrections are prepared by the Office of the Federal Register. Agency prepared corrections are issued as signed documents and appear in the appropriate document categories elsewhere in the issue.

ENVIRONMENTAL PROTECTION AGENCY

[OPP-180785; FRL-3427-4]

Emergency Exemptions

Correction

In notice document 88-18031 beginning on page 30092 in the issue of Wednesday, August 10, 1988, make the following corrections:

1. On page 30093, in the first column, in paragraph 29, in the eighth line, the date should read "April 6, 1988".

2. On the same page, in the second column, in the ninth line, "lettuce" was misspelled.

BILLING CODE 1505-01-D

ENVIRONMENTAL PROTECTION AGENCY

[OPP-50675A; FRL-3434-7]

Issuance of an Experimental Use Permit; Genetically Engineered Microbial Pesticide

Correction

In notice document 88-19301 beginning on page 32440 in the issue of Thursday, August 25, 1988, make the following correction:

On page 32440, in the third column, in the eighth line from the bottom, "5x1016" should read "$5x10^{16}$".

BILLING CODE 1505-01-D

ENVIRONMENTAL PROTECTION AGENCY

[OPTS-51710; FRL-3433-4]

Toxic and Hazardous Substances; Certain Chemicals Premanufacture Notices

Correction

In notice document 88-18955 beginning on page 31915 in the issue of Monday, August 22, 1988, make the following corrections:

1. On page 31916, in the second column, under **P 88-1619**, in the fourth line from the bottom, "toxicity" was misspelled.

2. On page 31917, in the second column, under **P 88-1641**, in the first line, "Hitachie" should read "Hitachi".

3. On page 31919, in the first column, under **P 88-1678**, in the third line, "bicyucloalkene" should read "bicycloalkene".

4. On page 31920, in the first column, under **P 88-1701**, in the second line, "4-(4-Methyl-e-" should read "4-(4-methyl-3-".

5. On the same page, in the third column, under **P 88-1714**, in the third line, "2,2,2-trifluor-4'-chloro-" should read "2,2,2-trifluoro-4'-chloro".

BILLING CODE 1505-01-D

GENERAL SERVICES ADMINISTRATION

48 CFR Parts 548 and 552

[GSAR Notice 5-257]

General Services Administration Acquisition Regulation; Value Engineering

Correction

In proposed rule document 88-19596 beginning on page 33155 in the issue of Tuesday, August 30, 1988, make the following correction:

On page 33156, in the first column, under **ADDRESS**, in the ninth line the phone number should read "(202) 523-3822".

BILLING CODE 1505-01-D

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 12

[Docket No. 87N-0364]

Formal Evidentiary Public Hearing; Time Periods for Filing Exceptions to Initial Decisions and Replies to Exceptions

Correction

In rule document 88-17708 appearing on page 29453 in the issue of Friday, August 5, 1988, make the following correction:

In the second column, in the seventh line from the bottom, "sec. 44(b)" should read "sec. 24(b)".

BILLING CODE 1505-01-D

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 86P-0510]

Canned Green Beans Deviating From Identity Standard; Extension and Amendment of Temporary Permit for Market Testing

Correction

In notice document 88-18328 appearing on page 30716 in the issue of Monday, August 15, 1988, make the following correction:

In the second column, on the first line, "(HHF-414)," should read "(HFF-414),.

BILLING CODE 1505-01-D

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 86P-0369]

Canned Pacific Salmon Deviating From Identity Standard; Extension of Temporary Marketing Permit

Correction

In notice document 88-18330 beginning on page 30716 in the issue of Monday, August 15, 1988, make the following correction:

On page 30716, in the third column, the Docket Number in the heading should appear as set forth above.

BILLING CODE 1505-01-D

SMALL BUSINESS ADMINISTRATION

13 CFR Part 115

[Revision 2]

Surety Bond Guarantee

Correction

In rule document 88-19168 beginning on page 32195 in the issue of Wednesday, August 24, 1988, make the following correction:

PART 115—CORRECTED]

Appendix B—[Corrected]

On page 32209, in the second column, in paragraph f. in the 4th and 5th lines, remove "Likewise, the file is to show subject contractor ,".

BILLING CODE 1505-01-D

DEPARTMENT OF TRANSPORTATION

Coast Guard

46 CFR Parts 31 and 91

[CGD 84-024]

RIN 2115-AB58

Intervals for Drydocking and Tailshaft Examination on Inspected Vessels

Correction

In rule document 88-18981 beginning on page 32225 in the issue of Wednesday, August 24, 1988, make the following corrections:

§ 31.10-21 [Corrected]

1. On page 32230, in § 31.10-21(a)(1), in Note 2 under table 31.10-21(a), in the first line, "internal" should read "external".

2. On the same page, in § 31.10-21(a)(2), in Note 2 under table 31.10-21(b), in the first line, "internal" should read "external".

§ 91.40-1 [Corrected]

3. On page 32231, in the third column, in amendatory instruction 16, in the fifth line, "(a)(20)" should read "(a)(2)".

BILLING CODE 1505-01-D

federal register

Thursday
September 8, 1988

Part II

Department of Transportation

Federal Aviation Administration

14 CFR Part 129

Operations: Foreign Air Carriers and Foreign Operators of U.S. Registered Aircraft Engaged in Common Carriage; Proposed Rulemaking

DEPARTMENT OF TRANSPORTATION

Federal Aviation Administration

14 CFR Part 129

[Docket No. 25693; Notice No. 88-14]
RIN 2120-AC42

Operations; Foreign Air Carriers and Foreign Operators of U.S.-Registered Aircraft Engaged in Common Carriage

AGENCY: Federal Aviation Administration (FAA), DOT.

ACTION: Notice of proposed rulemaking.

SUMMARY: This notice proposes to amend the foreign air carrier security regulations to require foreign air carriers, that land or take off in the United States, to submit to the FAA a written security program accetpable to the Administrator that describes the procedures, facilities, and equipment used by the foreign air carrier to provide for the safety of persons and property traveling in air transportation against acts of criminal violence and air piracy. This proposal is intended to ensure adequate security measures are being implemented by foreign air carriers who take off and land in the United States.

DATES: Comments must be received on or before November 7, 1988.

ADDRESSES: Comments on this notice are to be mailed in triplicate to: Federal Aviation Administration, Office of the Chief Counsel, Attention: Rules Docket (AGC-204), Docket No. 25693, 800 Independence Avenue, SW., Washington, DC 20591. Comments delivered must be marked Docket No. 25693. Comments may be inspected in the Rules Docket, Room 916, between 8:30 a.m. and 5:00 p.m. on weekdays, except Federal holidays.

FOR FURTHER INFORMATION CONTACT: Mr. David A. Smith, Domestic Civil Aviation Security Division (ACS-100), Federal Aviation Administration, 800 Independence Avenue, SW., Washington, DC 20591, telephone (202) 267-3947.

SUPPLEMENTARY INFORMATION:

Comments Invited

Interested persons are invited to participate in this proposed rulemaking by submitting such written data, views, or arguments as they may desire. Comments relating to the environmental, energy, or economic effects that might result from the adoption of the proposal contained in this notice are invited. Communications should identify the regulatory docket or notice number and be submitted in duplicate to the address listed above. Commenters wishing the FAA to acknowledge receipt of their comments submitted in response to this notice must submit with those comments a self-addressed, stamped postcard on which the following statement is made: "Comments to Docket No. 25693." The postcard will be date and time stamped and returned to the commenter. All communications received on or before the closing date for comments will be considered by the Administrator before taking action on the proposed rule. The proposals contained in this notice may be changed in light of comments received. All comments submitted will be available for examination in the Rules Docket both before and after the closing date for comments. A report summarizing each substantive public contact with FAA personnel concerned with this rulemaking will be filed in the docket.

Availability of NPRM

Any person may obtain a copy of this Notice of Proposed Rulemaking (NPRM) by submitting a request to the Federal Aviation Administration, Office of Public Affairs, Attention: Public Inquiry Center (APA-230), 800 Independence Avenue, SW., Washington, DC 20591, or by calling (202) 267-3484. Communications must identify the notice number of this NPRM. Persons interested in being placed on the mailing list for future NPRM's should also request a copy of Advisory Circular No. 11-2A, Notice of Proposed Rulemaking Distribution System, which describes the application procedures.

Background

Section 129.25(b) of the Federal Aviation Regulations (FAR) currently requires each foreign air carrier, that lands or takes off in the United States, to adopt and use a security program for each scheduled and public charter passenger operation as defined in § 129.25(a)(5) and (a)(6). Section 129.25(e) requires that each foreign carrier shall, upon the request of the Administrator and in accordance with applicable law, provide information regarding the implementation and operation of its security program.

These regulations were issued by the FAA in July 1975, consistent with its statutory responsibilities, at a time when aviation security had only recently become the focus of international attention. Indeed, at the time that the regulations were proposed, international standards on the subject of aviation security had yet to be adopted by the International Civil Aviation Organization (ICAO). The International Civil Aviation Organization adopted such standards and recommended practices in 1974, but their scope was rather limited.

Today, security is a major concern of the international aviation community. Terrorist activity against international civil aviation has increased and grown more sophisticated over the past decade. The United States has supported the many actions taken by ICAO in this area, including significant enhancements of the security standards and recommended practices contained in Annex 17 to the Convention on International Civil Aviation ("Chicago Convention").

On the bilateral front, the United States has negotiated comprehensive security articles in U.S. air transport agreements with many of our aviation partners. We are also continuously working with other countries to improve the level of international aviation security including technical assistance and consultations.

The United States also has taken its own steps to protect against the world-wide terrorist threat. In 1985, Congress enacted the International Security Development and Cooperation Act (Pub. L. 99-83) which, among other things, requires the Department of Transportation periodically to assess the effectiveness of security measures maintained at foreign airports being served by U.S. air carriers and those from which foreign air carriers serve the United States. This Act requires that the standard for evaluating these airports be based upon, at a minimum, the standards and appropriate recommended practices contained in Annex 17.

In light of our experience since the initial issuance of these regulations, and in light of developments in U.S. domestic legislation and the international standards and recommended practices, the FAA believes that it would be appropriate to amend Part 129. The regulations contained in Part 129 implement not only U.S. statutory requirements, but also the provisions of Annex 17 with respect to foreign air carriers operating to or from the United States. As such, Part 129 provides an important means by which to ensure that those operations comply with international and domestic requirements. As already discussed, the security requirements contained in Part 129 were issued when Annex 17, and domestic aviation security regulations, were in their infancy. There is now a need to make Part 129 more detailed and comprehensive to better reflect the enhancements made in international security requirements.

These changes are also necessary to make Part 129 more consistent with the provisions of the International Security and Development Cooperation Act. That Act, as noted, amended section 1115 of the Federal Aviation Act to require security assessments of foreign airports served by U.S. carriers and from which foreign carriers serve the United States. Evaluations of the effectiveness of the security measures used by those foreign carriers at those airports is integral to an airport assessment. The proposed amendments will provide a better means of assuring that the purpose of this provision of the Act is fulfilled.

This proposal, if adopted, would ensure that adequate security measures are being implemented by foreign air carriers with respect to operations to and from the United States by requiring that their security programs be acceptable to the Administrator. The proposed rule would be consistent with U.S. international obligations. Under the Chicago Convention and U.S. bilateral air transport agreements, foreign carriers are required to comply with the laws and regulations governing admission to or departure from the United States and the operation and navigation of those aircraft while within U.S. territory. The current provisions of Part 129 and the proposed changes are in the category of those laws and regulations. In addition, many of the U.S. bilateral air transport agreements contain specific provisions requiring compliance with ICAO and domestic provisions governing aviation security. The implementation of these proposals, if adopted, would be done in accordance with these international obligations.

If the FAA adopts this proposal, a model Standard Security Program, which meets the requirements of the final rule and is based on the international security provisions established by ICAO, will be prepared. It will be available to foreign carriers for implementation at foreign air carrier stations within the United States and at stations that are a last point of departure to landing in the United States. Future changes to these security programs, consistent with U.S. international obligations, may be necessary to continue to ensure that adequate security measures are being taken by foreign air carriers.

This proposal is not unique to the United States. Other countries, including Canada and the Federal Republic of Germany, require air carriers operating to or from their countries to provide security programs for review and approval.

Under this proposal, no foreign air carrier may land or take off in the United States from 90 days after the effective date unless the foreign air carrier has a security program acceptable to the Administrator. A foreign air carrier, currently conducting operations subject to this part, would be required to submit a proposed security program that meets the requirements of Part 129 to the Administrator no later than the effective date. It is anticipated that the effective date of the proposed rule would be 60 days after publication of the final rule in the **Federal Register**. The FAA does not anticipate that that this will impose a significant burden since foreign air carriers that land or take off in the United States and that meet the requirements of § 129.25(b) are required presently to adopt and use a security program; moreover, since a foreign air carrier is not required to have an acceptable security program until 90 days after the effective date, there should be adequate time in which to develop, modify, and submit a proposed security program. Unless otherwise authorized by the Administrator, foreign air carriers that want to begin operations after the effective date would be required to submit a proposed security program 90 days before passenger operations are scheduled to begin. Thereafter, the time schedules and procedures contained in this proposal would be followed for subsequent modifications of the foreign air carrier's security program. The proposed rule provides slightly extended timeframes from those contained in Part 108 of the Federal Aviation Regulations (FAR). The FAA invites comments on the proposed timeframes and appropriate alternatives.

Regulatory Evaluation

The proposal to amend Part 129 of the FAR would require each foreign air carrier, that lands or takes off in the United States, to submit a written security program to the FAA. These programs would be for implementation at foreign air carrier stations within the United States and stations that are the last point of departure prior to landing in the United States. The program would have to describe the procedures, facilities, and equipment used by the foreign air carrier to ensure the safety of passengers and property traveling on board its aircraft against acts of criminal violence and air piracy and be acceptable to the Administrator.

The FAA has determined that this proposal would affect the 111 foreign air carriers currently operating scheduled flights into the United States under Part 129. The regulatory evaluation prepared for this proposal estimates that the total cost of compliance to the affected 111 foreign air carriers with the security program requirements of this notice is $669,120 in 1986 dollars. An additional 200 entities, whose operations are not included in § 129.25(b), are involved in small aircraft charter and air taxi operations to the United States on a nonscheduled basis. They are not now required to have security programs, and this proposal would not require them to have security programs.

The primary benefits of this proposal would be the prevention of potential fatalities, injuries, and property losses resulting from criminal acts and acts of terrorism perpetrated against domestic and foreign aviation interests. The FAA has not been able to quantitatively estimate the extent to which these proposals will be effective in deterring acts of criminal violence and air piracy. The FAA believes, however, that the estimated $669,120 cost of compliance can be fully recovered if only one life, valued at $1,000,000, is saved as a result of the prevention of an act of criminal violence or air piracy. Hence, if one fatality is prevented as a result of this proposal during the 10-year period following implementation of the rule, the benefits of this proposal will be 1.5 times greater than the cost.

Regulatory Flexibility Determination

The FAA has determined that pursuant to the Regulatory Flexibility Act of 1980, the proposed amendment does not affect U.S. enterprises and therefore will not have a significant economic impact, positive or negative, on a substantial number of small domestic entities.

International Trade Impact Analysis

This proposal affects foreign air carriers operating under Part 129. The average onetime cost impact of $6,028 for each of the affected 111 foreign air carriers is considered negligible in comparison to the annual operating budgets of these carriers. Accordingly, this proposal, if adopted, would have little or no impact on trade opportunities for U.S. firms doing business overseas or for foreign firms doing business in the United States. Also, U.S. air carriers operating to foreign destinations already have detailed security programs fully implemented; therefore, should any foreign government apply a similar requirement as a result of this rule, costs to U.S. air carriers would be small.

Paperwork Reduction Act Approval

Section 129.25(e)(1) would require each foreign air carrier landing or taking off in the United States to submit a security program acceptable to the

Administrator to the FAA. In accordance with the Paperwork Reduction Act of 1980 (Pub. L. 96-511), the recordkeeping and reporting provisions contained in this NPRM have been submitted for approval to the Office of Management and Budget (OMB). Comments on these requirements should be submitted to the Office of Information and Regulatory Affairs (OMB), New Executive Office Building, Room 3001, Washington, DC 20503; Attention: FAA Desk Officer, telephone (202) 395-7340. A copy should be submitted to the FAA docket.

Federalism Implications

The regulations proposed herein would not have substantial direct effects on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Thus, in accordance with Executive Order 12612, it is determined that such regulation does not have federalism implications warranting the preparation of a Federalism Assessment.

Conclusion

For the reasons discussed in the preamble, and based on the findings in the Regulatory Flexibility Determination and the International Trade Impact Analysis, the FAA has determined that this proposed regulation is not major under Executive Order 12291. Additionally, this proposal, if adopted, will not have a significant economic impact, positive or negative, on a substantial number of small entities under the criteria of the Regulatory Flexibility Act. This proposal is considered significant under DOT Regulatory Policies and Procedures (44 FR 11034; February 26, 1979). An initial regulatory evaluation of the proposal, including a Regulatory Flexibility Determination and Trade Impact Analysis, has been placed in the docket. A copy may be obtained by contacting the person identified under "**FOR FURTHER INFORMATION CONTACT.**"

List of Subjects in 14 CFR Part 129

Aircraft, Air carrier, Airports, Aviation safety, Weapons.

The Proposed Amendments

In consideration of the foregoing, the FAA proposes to amend Part 129 of the Federal Aviation Regulations (14 CFR Part 129) as follows:

PART 129—OPERATIONS: FOREIGN AIR CARRIERS AND FOREIGN OPERATORS OF U.S.-REGISTERED AIRCRAFT ENGAGED IN COMMON CARRIAGE

1. The authority citation for Part 129 continues to read as follows:

Authority: 49 U.S.C. 1346, 1354(a), 1356, 1357, 1421, 1502, and 1511; 49 U.S.C. 106(g) (Revised Pub. L. 97-449, January 12, 1983).

2. Section 129.25 is amended by revising paragraph (b) introductory text, paragraph (b)(2), the introductory text of paragraph (c), paragraphs (d) and (e) to read as follows:

§ 129.25 Airplane security.

* * * * *

(b) After December 7, 1988, each foreign air carrier landing or taking off in the United States shall adopt and use a security program, acceptable to the Administrator, for each scheduled and public charter passenger operation, that meets the requirements of—

* * * * *

(2) Paragraph (c) of this section for each operation that will provide deplaned passengers access to a sterile area, if that access is not controlled by a certificate holder using an approved security program or a foreign air carrier using a security program acceptable to the Administrator required by this section;

* * * * *

(c) After December 7, 1988, in order to be acceptable to the Administrator, each security program required by paragraph (b) (1), (2), or (3) of this section must be designed to—

* * * * *

(d) After December 7, 1988, in order to be acceptable to the Administrator, each security program required by paragraph (b)(4) of this section must include the procedures used to comply with the applicable requirements of paragraph (h)(2) and (i) of this section regarding law enforcement officers.

(e) The following procedures apply for acceptance of a security program by the Administrator:

(1) Unless otherwise authorized by the Administrator, each foreign air carrier required to have a security program by paragraph (b) of this section shall submit its proposed security program to the Administrator by [effective date] or at least 90 days before the intended date of passenger operations, whichever is later. The proposed security program must be in English unless the Administrator requests that the proposed program be submitted in the official language of the foreign air carrier's country. The Administrator will notify the foreign air carrier of the security program's acceptability, or the need to modify the proposed security program for it to be acceptable under this part, within 30 days after receiving the proposed security program. The foreign air carrier may petition the Administrator to reconsider the notice to modify the security program within 30 days after receiving the notice to modify.

(2) In the case of a security program previously found to be acceptable, the Administrator may subsequently find that the program will become unacceptable unless appropriate revisions are made in the interest of safety in air transportation or in air commerce and in the public interest within a specified period of time. In making such a finding the following procedures apply:

(i) The Administrator notifies the foreign air carrier, in writing, of a proposed finding of unacceptability, fixing a period of not less than 45 days within which the foreign air carrier may submit written information, views, and arguments on the proposed finding.

(ii) At the end of the comment period, after considering all relevant material, either the Administrator issues a finding of unacceptability, specifying appropriate revisions to make the program acceptable, or rescinds the proposed finding. If the Administrator issues a finding of unacceptability, the program becomes unacceptable 45 days thereafter, unless the foreign air carrier either—

(A) Revises the program so that it becomes acceptable to the Administrator and submits the revised program to the Administrator; or

(B) Petitions the Administrator to reconsider the finding of unacceptability, in which case the program remains unaccepable until the Administrator reconsiders the matter.

(3) If the Administrator finds that there is an emergency requiring immediate action with respect to safety in air transportation or in air commerce, the Administrator may issue an emergency notice of unacceptability. In such a case, the Administrator incorporates in the notice the finding of unacceptability, a brief statement of the reasons for the proposed revision, and appropriate revisions that would make the security program acceptable to the Administrator. The security program is considered to be unacceptable when the foreign air carrier receives the emergency notice of unacceptability unless immediate revisions are made to the security program. To ensure acceptability of the revision, the foreign

air carrier must submit a copy of it to the Administrator.

(4) A foreign air carrier must submit any amendments to its security program to the Administrator for a finding of acceptability. The proposed amendment must be filed with the Administrator at least 45 days before the date the foreign air carrier proposes for the amendment to become effective, unless a shorter period is allowed by the Administrator. Within 30 days after receiving a proposed amendment, the Administrator will notify the foreign air carrier whether the amendment is acceptable. The foreign air carrier may petition the Administrator to reconsider a notice of unacceptability of the proposed amendment within 45 days after receiving notice of unacceptability.

* * * * *

Issued in Washington, DC on August 31, 1988.

Raymond A. Salazar,

Director of Civil Aviation Security.

[FR Doc. 88-20319 Filed 9-7-88; 8:45 am]

BILLING CODE 4910-13-M

federal register

Thursday
September 8, 1988

Part III

Department of Education

Office of Special Education And Rehabilitative Services

National Institute on Disability and Rehabilitative Research; Consolidated Application Package; Fiscal Year 1989; Notice Inviting Applications

DEPARTMENT OF EDUCATION

Office of Special Education and Rehabilitative Services

National Institute on Disability and Rehabilitation Research; Consolidated Application Package; Fiscal Year 1989

AGENCY: Department of Education.

ACTION: Notice inviting applications for new awards under certain programs.

SUMMARY: The Secretary invites applications for new awards under the Rehabilitation Research and Training Center (RRTC) program, the Career Development and Research Training program, the Field-Initiated Research Projects program, the Innovation Grants program, and the Research Fellowship program of the National Institute on Disability and Rehabilitation Research (NIDRR).

This notice consists of four sections. Section I provides background information. Section II contains four lists of program application notices and application information that pertains to the programs in each list. Section III provides further guidance on the application process. Section IV contains the basic application forms and instructions for completing the forms. No separate application package is necessary to apply for awards under the programs announced in this notice.

DATES: The closing dates for transmitting applications under this notice are listed in Section II of this notice.

ADDRESS: Applications are to be mailed to the following address: U.S. Department of Education, 400 Maryland Avenue, SW., Application Control Center, Washington, DC 20202–4725. See Section III for detailed information related to hand-delivered applications.

FOR FURTHER INFORMATION CONTACT: The National Institute on Disability and Rehabilitation Research, 400 Maryland Avenue, SW., Washington DC 20202. Telephone: (202) 732–1207; deaf and hearing impaired-persons may call (202) 732–1198 for TDD service.

SUPPLEMENTARY INFORMATION: The publication of these closing dates or these estimated founding levels does not bind the Department of Education to make awards in any of these categories, or to any specific number of awards or funding levels, unless otherwise specified in statute.

Paperwork Reduction Act of 1980

This combined application package contains no new information collection requirements. The information collection requirements contained herein have been approved by the Office of Management and Budget (OMB) under Control Number 1820–0027.

Section I—General

Application closing dates are listed in Section II of this notice. Closing dates and procedures may vary from program to program. The chart in Section II informs potential applicants of: Program titles; Catalog of Federal Domestic Assistance (CFDA) number; deadline for transmittal of applications (closing date); estimated available funds; estimated number of awards; estimated range of awards; estimated size of awards; and expected project period.

This notice also contains a detailed description of the RRTC on Rehabilitation in the Pacific Basin, in accordance with the provisions of the Rehabilitation Act Amendments of 1986. Prospective applicants for that award under the RRTC program should prepare their applications based on that description. Interested parties should be aware that the Secretary intends to publish proposed and final priorities for other RRTC awards in a separate issue of the **Federal Register.**

Applicants may apply for awards under more than one program, and may apply for more than one award within a given program. However, applicants must submit a complete and separate application for each individual award for which they are applying. To ensure expeditious processing of their respective applications, applicants are particularly requested to make certain that the correct CFDA number for the program appears on each application. Following the chart is the specific program information on: the purpose of each program, applicable regulations, information contact persons, and any other program information and specific application requirements not covered in the application form in Section IV.

Section II—Program Application Notices

This section contains (1) a listing of application notices for new awards for fiscal year 1989, and (2) specific application information and requirements for individual programs.

NATIONAL INSTITUTE ON DISABILITY AND REHABILITATION RESEARCH INFORMATION FOR TRANSMITTAL OF APPLICATIONS UNDER CERTAIN PROGRAMS FOR FISCAL YEAR 1989

CFDA No.	Program title	Deadline for transmittal of applications	Estimated available funds	Estimated number of awards	Estimated range of awards	Estimated average award	Project period (in months)
84.133B	Rehabilitation Research and Training Center.	11–02–88	$700,00	1	$750,000	$750,000	Up to 60.
84.133C	Innovation Grants Program	6–01–89	750,000	20	$50,000	$50,000	Up to 12.
84.133F	Research Fellowships	12–02–88	300,000	10	$25,000 plus $30,000 plus $1,500 expenses.	$27,500 plus $1,500 expenses.	Up to 12.
84.133G	Field-Initiated	11–30–88	2,000,000	20	$75,000 to $125,000	$100,000	Up to 36.
84.133P	Career Development Research Training.	11–02–88	375,000	3	$100,000 to $125,000	$125,000	Up to 36.

Title of Program: Rehabilitation Research and Training Centers

CFDA No.: 84.133B

Purpose: Rehabilitation Research and Training Centers (RRTCs) conduct coordinated and advanced programs of rehabilitation research, provide training—including undergraduate, graduate, and in-service training—to research and other rehabilitation personnel, and assist individuals to more effectively provide rehabilitation services.

Applicable Regulations: (a) The regulations governing the RRTC program at 34 CFR Parts 350 and 352, and (b) the Education Department General Administrative Regulations at 34 CFR Parts 74, 75, 77, 78 and 80.

Contact Person: L. Deno Reed, National Institute on Disability and Rehabilitation Research, 400 Maryland Avenue, SW., Washington, DC. 20202. Telephone (202) 732–1193; deaf and hearing-impaired persons may call (202) 732–1198 for TDD services.

Program Authority: 20 U.S.C. 762(b)(1)

Supplementary Information and Requirements

Eligible Applicans: Under this program, awards are made to institutions of higher education, or to public or private agencies or organizations, including Indian tribes and tribal organizations, in affiliation with institutions of higher education. Applicant institutions need not be located currently in the Pacific Basin. However, clinical research, training, and other Center activities must be carried out in the Pacific Basin.

Special Requirements: The RRTC to be funded under this notice is for *Research on Rehabilitation Problems in the Pacific Basin.* In the Rehabilitation Act Amendments of 1984 (Pub. L.90–221), the Congress mandated that NIDRR establish a Research and Training Center in the Pacific Basin.

In the Rehabilitation Act Amendments of 1986 (Pub. L. 99–506), the Congress further specified a scope of work for the Pacific Basin Center. The RRTC, in addition to meeting the statutory and regulatory requirements for all RRTCs must address effectively the following activities specified in the Rehabilitation Act Amendments of 1986:

- Develop a sound demographic database on the distribution of disabilities and related factors among various groups and localities in the region;
- Analyze, develop, and promote the utlization of appropriate technology to aid disabled persons;
- Develop a culturally relevant program to train personnel in the provision of rehabilitation services;
- Facilitate interagency communication and cooperation among rehabilitation-related agencies in the Pacific Basin and between the RRTC and other rehabilitation information resources, using advanced information technology; and
- Develop appropriate rehabilitation interventions and cost-effective service delivery models to improve rehabilitation in the Pacific Basin.

Selection Criteria: The Secretary uses the following criteria in 34 CFR 352.31 to evaluate an application under this program.

(a) *Relevance and importance of the research program.* (20 points)

The Secretary reviews each application to determine to what degree—

(1) The proposed activities are responsive to a priority established by the Secretary and address a significant need of a disabled target population and rehabilitation service providers;

(2) The overall research program of the Center includes appropriate interdisciplinary and collaborative research activities, is likely to lead to new and useful knowledge in the priority area, and is likely to become a nationally recognized source of scientific knowledge; and

(3) The applicant demonstrates that all component activities of the Center are related to the overall objective of the Center, and will build upon and complement each other to enhance the likelihood of solving significant rehabilitation problems.

(b) *Quality of the Research design.* (35 points) The Secretary reviews each application to determine to what degree—

(1) The applicant proposes a comprehensive research program for the entire project period, including at least three interrelated research projects;

(2) The research design and methodology of each proposed activity are meritorious in that—

(i) The literature review is appropriate and indicates familiarity with current research in the field;

(ii) The research hypotheses are important and scientifically relevant;

(iii) The sample populations are appropriate and significant;

(iv) The data collection and measurement techniques are appropriate and likely to be effective;

(v) The data analysis methods are appropriate; and

(vi) The applicant assures that human subjects, animals, and the environment are adequately protected; and

(3) The application discusses the anticipated research results and demonstrates how those results would satisfy the original hypotheses and could be used for planning future research, including generation of new hypotheses where applicable.

(c) *Quality of the training and dissemination program.* (25 points): The Secretary reviews each application to determine the degree to which—

(1) The proposed plan for training and dissemination provides evidence that research results will be effectively disseminated and utilized based on the identification of appropriate and accessible target groups; the proposed training materials and methods are appropriate; the proposed activities are relevant to the regional and national needs of the rehabilitation field; and the training materials and dissemination packages will be developed in alternate media that are usable by people with various types of disabilities.

(2) The proposed plan for training and dissemination provides for—

(i) Advanced training in rehabilitation research;

(ii) Training rehabilitation service personnel and other appropriate individuals to improve practitioner skills based on new knowledge derived from research;

(iii) Training packages that make research results available to service providers, researchers, educators, disabled individuals, parents, and others;

(iv) Technical assistance or consultation that is responsive to the concerns of service providers and consumers; and

(v) Dissemination of research findings through publication in professional journals, textbooks, and consumer and other publications, and through other appropriate media such as audiovisual materials and telecommunications.

(d) *Quality of the organization and management. (20 points):* The Secretary reviews each application to determine the degree to which—

(1) The staffing plan for the Center provides evidence that the project director, research director, training director, principal investigators, and other personnel have appropriate training and experience in disciplines required to conduct the proposed activities; the commitment of staff time is adequate to conduct all proposed activities; and the Center, as part of its nondiscriminatory employment practices, will ensure that its personnel are selected for employment without regard to race, color, national origin, gender, age, or handicapping condition.

(2) The budgets for the Center and for each component project are reasonable, adequate, and cost-effective for the proposed activities;

(3) The facilities, equipment, and other resources are adequate and are appropriately accessible to persons with disabilities;

(4) The plan of operators is adequate to accomplish the Center's objectives and to ensure proper and efficient manangement of the Center;

(5) The proposed relationships with Federal, State, and local rehabilitation service providers and consumer organizations are likely to ensure that the Center program is relevant and

applicable to the needs of consumers and service providers;

(6) The past performance and accomplishments of the applicant indicate an ability to complete successfully the proposed scope of work;

(7) The application demonstrates appropriate commitment and support by the host institution and opportunities for interdisciplinary activities and collaboration with other institutions and organizations; and

(8) The plan for evaluation of the Center provides for an annual assessment of the outcomes of the research, the impact of the training and dissemination activities on the target populations, and the extent to which the overall objectives have been accomplished.

Title of Program: Innovation Grants Program

CFDA No.: 84.133C

Purpose: This program is designed to provide financial support to projects that: (a) Test new concepts and innovative ideas; (b) demonstrate research results of high potential benefits; (c) purchase and evaluate prototype aids and devices; (d) develop unique rehabilitation training curricula; (e) conduct feasibility, planning, and evaluation studies and conferences, and other activities to disseminate specific research findings.

Applicable Regulations: (a) Program regulations at 34 CFR Parts 350 and 358, and (b) the Education Department General Administrative Regulations, 34 CFR Parts 74, 75, 77, 78, and 80.

Contact Person: National Institute on Disability and Rehabilitation Research, 400 Maryland Avenue, SW., Washington, DC 20002. Telephone: (202) 732–1207; deaf and hearing-impaired individuals may call (202) 732–1198 for TDD services.

Program Authority: 29 U.S.C. 762(b)(13)

Supplementary Information and Requirements

Eligible Applicants: Public and private nonprofit and for-profit agencies and organizations, institutions of higher education, and Indian tribes and tribal organizations are eligible to apply for awards under this program.

Selection Criteria: The Secretary evaluates applications under this program according to the following selection criteria in 34 CFR 358.31.

(a) *Importance of the project (50 points):* The Secretary reviews each application to determine to what degree the proposed activity will address a significant need of the target population and will meet the purpose of this part.

(b) *Project design or methodology (25 points).* The Secretary reviews each application to determine to what degree the underlying hypothesis or conceptual model is sound; the project design is likely to achieve the desired objectives; and the evaluation plan is appropriate.

(c) *Plan of operation (25 points).* The Secretary reviews each application to determine the extent to which the qualifications and background of the key personnel, the management and financial plan, and the capability and resources of the applicant organization demonstrate that the applicant will be able to carry out the proposed project.

Title of Program: Research Fellowships

CFDA No.: 84.133F

Purpose: The purpose of this program is to build research capacity by providing support to highly qualified individuals to perform research on the rehabilitation of disabled persons.

Applicable Regulations: The regulations in 34 CFR Parts 350 and 356 are applicable to this program.

Contact Person: Joseph Fenton, National Institute on Disability and Rehabilitation Research, 400 Maryland Avenue SW., Washington, DC 20202. Telephone: (202) 732–1143; deaf and hearing-impaired individuals may call (202) 732–1198 for TDD services.

Program Authority: 29 U.S.C. 761a(d)

Supplementary Information and Requirements

Eligible Applicants: Only individuals are eligible to apply for research fellowships under this program.

Selection Criteria: The Secretary evaluates applications for fellowships according to the following criteria in 34 CFR 356.30.

(a) Quality and level of formal education, previous work experience, and recommendations of present or former supervisors or colleagues that include an indication of the applicant's ability to work creatively in scientific research; and

(b) The quality of a research proposal of no more than 12 pages containing the following information:

(1) The importance of the problem to be investigated to the purpose of the Act and the mission of NIDRR.

(2) The research hypotheses or related objectives and the methodology and design to be followed.

(3) Assurance of the availability of any necessary data resources, equipment, or institutional support, including technical consultation and support where appropriate, required to carry out the proposed activity.

Title of Program: Field-Initiated Research Projects

CFDA No.: 84.133G

Purpose: This program is designed—(a) To encourage eligible parties to originate valuable ideas for research and demonstration, development, or knowledge dissemination projects to improve the lives of individuals with disabilities, and (b) to support research and demonstration, development, or knowledge dissemination projects as described in program regulations that address important activities not supported by Institute-funded research or that complement that research in a promising way.

Applicable Regulations: (a) The regulations governing this program in 34 CFR Parts 350 and 357; (b) the Education Department General Administrative Regulations, 34 CFR Parts 74, 75, 77, 78, and 80.

Contact: National Institute on Disability and Rehabilitation Research, 400 Maryland Avenue SW., Washington, DC 20002. Telephone: (202) 732–1207; deaf and hearing impaired individuals may call (202) 732–1198 for TDD services.

Program Authority: 29 U.S.C. 762.

Supplementary Information and Requirements

Eligible Applicants: Parties eligible to apply for grants under this program are public and private for-profit or nonprofit agencies and organizations, including institutions of higher education and Indian tribes or tribal organizations.

Selection Criteria: The Secretary uses the following criteria in 34 CFR 357.32 to evaluate an application under this program.

(a) *Importance of the problem.* (20 points) The Secretary reviews each application to determine the extent to which—

(1) The proposed project addresses a problem that is significant to persons with disabilities or to those who provide services to them; and

(2) The proposed project is likely to produce new and useful knowledge, techniques, or devices that will develop or disseminate solutions to problems confronting persons with disabilities.

(b) *Design of the project.* (45 points)

(1) The Secretary reviews each application for a research and demonstration project to determine the extent to which—

(i) The review of the literature is appropriate and indicates familiarity with the relevant current research;

(ii) The research hypotheses are theoretically sound and based on current knowledge;

(iii) The sample populations are adequate and appropriately selected;

(iv) The data collection instruments and methods are appropriate and likely to be successful;

(v) The data analysis measures are appropriate; and

(vi) The application discusses the anticipated research results and demonstrates how those results would satisfy the original hypotheses.

(2) The Secretary reviews each application for a knowledge dissemination project to determine the extent to which—

(i) The need for the information has been demonstrated;

(ii) The target populations are appropriately specified;

(iii) The dissemination methods are appropriate to the target populations;

(iv) The materials for dissemination are prepared in media accessible to the target population;

(v) There are adequate means of documenting and evaluating the effectiveness of the dissemination activity.

(3) The Secretary reviews each application for a development project to determine the extent to which—

(i) The proposed project will use the most effective and appropriate technology available in developing the new device or technique;

(ii) The proposed development is based on a sound conceptual model that demonstrates an awareness of the state-of-the-art in technology;

(iii) Devices or techniques will be developed and tested in an appropriate environment;

(iv) The applicant considers the cost-effectiveness and usefulness of the device or technique to be developed for persons with disabilities; and

(v) The applicant discusses the potential for commercial or private manufacture, marketing, and distribution of the product.

(c) *Personnel.* (20 points) The Secretary reviews each application to determine the extent to which—

(1) The key personnel have adequate training and experience in the required discipline to conduct the proposed activities;

(2) The allotment of staff time is adequate to accomplish the proposed activities; and

(3) The applicant ensures that personnel are selected for employment without regard to race, color, national origin, gender, age, or handicapping conditions.

(d) *Management and Evaluation.* (15 points) The Secretary reviews each application to determine the extent to which—

(1) The resources of the applicant are adequate, appropriate, and accessible to individuals with disabilities;

(2) The proposed budget is adequate and appropriate for the activities to be carried out;

(3) There is a plan, appropriate to the type of field-initiated project, to evaluate the effectiveness of the project in accomplishing its goals and objectives;

(4) The applicant provides a plan of operations, appropriate to the type of field-initiated project, indicating that it will achieve the project objectives in a timely and effective manner; and

(5) Appropriate collaboration with other agencies is assured.

Title of Program: Career Development and Research Training Grants Program

CFDA No.: 84.133P

Purpose: The purpose of this program is to expand capability in the field of rehabilitation research by supporting projects that provide advanced training in rehabilitation research. These projects provide research training and experience at an advanced level to individuals with doctorates or similar advanced degrees who have clinical or other relevant experience, including experience in management or basic science research, in fields pertinent to rehabilitation in order to qualify those individuals to conduct independent research on problems related to disability and rehabilitation.

Applicable Regulations: (a) Regulations governing this program in 34 CFR Parts 350 and 360, and (b) the Education Department General Administrative Regulations in 34 CFR Parts 74, 75, 77, and 78.

Contact Person: Inez Storck, National Institute on Disability and Rehabilitation Research, 400 Maryland Avenue SW., Washington, DC 20202–2646. Telephone: (202) 732–1202; deaf and hearing-impaired individuals may call (202) 732–1198 for TDD services.

Program Authority: 29 U.S.C. 761(a)(k).

Supplementary Information and Requirements

Eligible Applicants: Institutions of higher education are eligible to receive assistance under this program.

Selection Criteria: The Secretary uses the following criteria in 34 CFR 360.31 to evaluate applications under this program.

(a) *Importance and potential contribution.* (20 points) The Secretary reviews each application to determine to what degree—

(1) The applicant is responsive to any priority established under §360.32;

(2) The applicant proposes to provide training in a rehabilitation discipline or area of study in which there is a shortage of qualified researchers, or to provide training to a trainee population in which there is a need for more qualified researchers, such as clinicians in rural areas, or clinicians who are directly experienced with underserved populations; and

(3) The applicant is likely to make a significant increase in the number of trained rehabilitation researchers.

(b) *Quality of proposed training program.* (40 points) The Secretary reviews each application to determine to what degree—

(1) The applicant's proposed recruitment program is likely to be effective in recruiting highly qualified trainees;

(2) The proposed didactic and classroom training programs emphasize scientific methodology, are multidisciplinary, comprehensive, and appropriate to the level of the trainees, and are likely to produce qualified independent researchers;

(3) The quality and extent of the academic mentorship, guidance, and supervision to be provided to each individual trainee are of a high level and are likely to produce highly qualified researchers;

(4) The type, extent, and quality of the proposed clinical and laboratory research experience, including the opportunity to participate in research on meaningful topics at an advanced level, are likely to develop individuals with the capacity to perform independent research; and

(5) The opportunities for collegial and collaborative activities, exposure to outstanding scientists in the field, and opportunities to participate in the preparation of scholarly or scientific publications and presentations are extensive and appropriate.

(c) *Personnel and resources committed to the project.* (30 points) The Secretary evaluates each application to determine to what degree—

(1) The activities of the project will be implemented by sufficient and qualified staff who are outstanding scientists in the field;

(2) The project director and other key staff are experienced in the delivery of advanced research training as well as knowledgeable about the methodology and literature of pertinent subject areas;

(3) All required disciplines are effectively included; and

(4) The applicant possesses the appropriate facilities, laboratories, and

access to clinical populations and organizations representing persons with disabilities to support the conduct of advanced clinical rehabilitation research.

(d) *Management and operating plans.* (10 points) The Secretary evaluates each application to determine to what degree—

(1) There is an effective plan of operation that ensures proper and efficient administration of the project;

(2) There is an effective plan for collaboration with other institutions of higher education and organizations whose participation is necessary to ensure effective classroom and clinical research training;

(3) The applicant, as part of its nondiscriminatory employment practices, will ensure that its personnel are selected without regard to race, color, national origin, gender, age, or handicapping condition;

(4) The applicant has provided an adequate plan for the use of facilities, resources, supplies, and equipment;

(5) The budget for the project is reasonable and adequate to support the proposed activities; and

(6) The applicant provides an appropriate plan for the evaluation of all phases of the project.

Section III—Instructions for Transmittal of Applications

Applicants are advised to reproduce and complete the application forms in Section IV. Applicants are required to submit an original and two copies of each application as provided in this Section.

Application Delivered by Mail

An application sent by mail must be addressed to the U.S. Department of Education, 400 Maryland Avenue SW., Application Control Center, Attention: (Appropriate CFDA No.), Washington, DC 20202.

An applicant must show proof of mailing consisting of one of the following:

(1) A legibly dated U.S. Postal Service postmark.

(2) A legible mail receipt with the date of mailing stamped by the U.S. Postal Service.

(3) A dated shipping label, invoice, or receipt from a commercial carrier.

(4) Any other proof of mailing acceptable to the Secretary of Education. If an application is sent through the U.S. Postal Service, the Secretary does not accept either of the following as proof of mailing: (1) A private meter postmark, or (2) a mail receipt that is not dated by the U.S. Postal Service.

An applicant should note that the U.S. Postal Service does not uniformly provide a dated postmark. Before relying on this method, an applicant should check with its local post office.

An applicant is encouraged to use registered or at least first class mail. Each late applicant will be notified that its application will not be considered.

Applications Delivered by Hand

An application that is hand-delivered must be taken to the U.S. Department of Education, Application Control Center, Room 3633, Regional Office Building #3, 7th and D Streets SW., Washington, DC.

The Application Control Center will accept hand-delivered applications between the hours of 8:00 a.m. and 4:30 p.m. (Washington, DC time) daily, except Saturdays, Sundays and Federal holidays.

An application that is hand-delivered will not be accepted after 4:30 p.m. on the closing date.

Authority: 29 U.S.C. 760–762.

(Catalog of Federal Domestic Assistance Nos. 84.133B, 84.133C, 84.133F, 84.133G, and 84.133P, National Institute on Disability and Rehabilitation Research)

Dated: August 30, 1988.

Patricia McGill Smith,

Deputy Assistant Secretary, Office of Special Education and Rehabilitative Services.

Frequent Questions

NIDRR staff are frequently asked to clarify or expand on information that is included in the application materials and the notices published in the **Federal Register.** In order to simplify this process for potential applicants and staff alike, the Institute discusses on the following pages some of the issues that these application materials frequently engender.

These questions are representative of those that are frequently raised, even though in many cases they are answered in the notices or application instructions. However, it appears that some of these issues are not explained sufficiently in the published notices, and that the requirements applying to the number of new and different NIDRR programs are confusing.

These questions and answers are meant to be informative, and are not regulatory requirements in and of themselves.

1. Can I Get An Extension of the Due Date?

No! On rare occasions the Department of Education may extend a closing date for all applicants. If that occurs, a notice of the revised due date is published in the **Federal Register.** However, there are no extensions or exceptions to the due date made for individual applicants.

Further information about mailing is included in Section IV of this Consolidated Application Package.

2. What Should Be Included in the Application?

The applicant should include the materials specified in Section IV of this Consolidated Application Package. Specifically, the application should include a project narrative, vitae of key personnel, and a budget, as well as the Assurances forms included in this package. Vitae of staff or consultants should include the individual's title and role in the proposed project, and other information that is specifically pertinent to this proposed project. The budgets for both the first year and subsequent project years should be included.

If collaboration with another organization is involved in the proposed activity, the application should include assurances of participation by the other parties, including written agreements or assurances of cooperation.

It is *not* useful to include general letters of support or endorsement in the application.

If the applicant proposes to use unique tests or other measurement instruments that are not widely known in the field, it would be helpful to include the instrument in the application.

Many applications contain voluminous appendices that are helpful and in many cases cannot even be mailed to the reviewers. It is generally not helpful to include such things as brochures, general capability statements of collaborating organizations, maps, copies of publications, or descriptions of other projects completed by the applicant.

3. What Format Should Be Used for the Application?

NIDRR generally advises applicants that they may organize the application to follow the selection criteria that will be used. The specific review criteria vary according to the specific program, and are contained in this Consolidated Application Package.

4. May I Submit Applications to More Than One Program Competition in NIDRR or More Than One Application to a Program?

Yes, you may submit applications to any program for which they are responsive to the program requirements. You may submit the same application to as many competitions as you believe appropriate. You may also submit more

than one application in any given competition.

5. What is the Allowable Indirect Cost Rate?

The limits on indirect costs vary according to the program and the type of application.

Applications for Rehabilitation Research and Training Centers should limit indirect cost rates to fifteen percent of the grant award, as noted in the program regulations and statute.

Applications in other programs that are for training activities should limit indirect charges to the lesser of the actual indirect costs or eight percent of the total direct costs of the program, as noted in the Education Department General Administrative Regulations (EDGAR).

All other applicants should limit indirect charges to the organization's approved rate. If the organization does not have an approved rate, the application should include an estimated actual rate.

6. Can Profitmaking Businesses Apply for Grants?

Yes. However, for-profit organizations will not be able to collect a fee or profit on the grant, and in some programs will be required to share in the costs of the project.

7. Can Individuals Apply for Grants?

No. Only organizations are eligible to apply for grants under NIDRR programs.

8. Can Universities Apply Under the Fellowship Program?

No. Only individuals are eligible to apply for fellowships under the regulations governing that program.

9. Is there a Cost-Sharing or Matching Requirement?

Cost-sharing is required in the Research and Demonstration Projects program, with certain exceptions noted in the law, the Knowledge Dissemination and Utilization program, the Field-Initiated Research program, and the Career Development and Research Training program.

There are no cost-sharing requirements for the Innovation Grants or the Research Fellowship programs.

For the Rehabilitation Research and Training Centers and the Rehabilitation Engineering Centers, the Secretary has the option to require matching. It is generally the practice of the agency to require cost-sharing under these programs.

There is no set rate for cost-sharing. The cost-sharing is negotiated at the time an award is made and is not part of the evaluation of the application.

10. What Are the Priorities in the Field-Initiated or Innovation Grants Programs?

There are no priorities in either the Field-Initiated Research or Innovation Grants programs. Applicants are free to submit applications in areas of interest to the investigator as long as they are related to the purposes of the program as described in the regulations.

11. Can NIDRR Staff Advise Me Whether My Project Is of Interest to NIDRR or Likely To Be Funded?

No. NIDRR staff can advise you of the requirements of the program in which you propose to submit your application. However, staff cannot advise you of whether your subject area is likely to receive approval in the investigator-initiated competitions.

12. How Do I Assure That My Application Will Be Referred to the Most Appropriate Panel for Review?

Applicants should be sure that their applications are referred to the correct competitions by clearly including the competition title and CFDA number, including alphabetical code, on the Standard Form 424.

Applicants should assist NIDRR in ensuring that their Field-Initiated and Innovation Grant applications are referred to the most appropriate panels by emphasizing the focus of the proposed activity in the abstract of the project on the Standard Form 424. It would be helpful if the applicant would not use acronyms in the title and abstract, unless those acronyms are in common usage nationally.

13. How Soon After Submitting My Application Can I Find Out if it Will Be Funded?

The time from closing date to grant award date varies from program to program and for other reasons. Generally speaking, NIDRR endeavors to have awards made within five to six months of the closing date. Unsuccessful applicants generally will be notified within that time frame as well. For the purpose of estimating a project start date, the applicant should estimate approximately six months from the closing date, but no later than the following September 30.

14. Can I Call NIDRR To Find Out if My Application Is Being Funded?

No! When NIDRR is able to release information on the status of grant applications, it will notify applicants by letter. The results of the peer review cannot be released except through this formal notification.

15. If My Application Is Successful, Can I Assume I Will Get the Requested Budget Amount in Subsequent Years?

No. Those budget projections are necessary and helpful for planning purposes. However, a complete budget and budget justification must be submitted for each year of the project and there will be negotiations on the budget each year.

16. Will All Approved Applications Be Funded?

No. It often happens that the peer review panels approve for funding more applications than NIDRR can fund within available resources. Applicants who are approved but not funded are encouraged to consider submitting similar applications in future competitions.

Section IV Application Instructions and Forms

This application is divided into three parts. These parts are organized in the same manner that the submitted application should be organized. The parts are as follows:

Part I: Federal Assistance Face Sheet (Form SF 424) and instructions
Part II: Budget Information
Part III: Application Narrative

No grants may be awarded unless a completed application form has been received. (20 U.S.C. 1021, 1041; 34 CFR Part 778)

Submit the original and two copies to:

Mailing Address: U.S. Department of Education, Application Control Center, Attention: (CFDA #), 400 Maryland Avenue, SW., Washington, DC 20202

Hand Delivery: U.S. Department of Education, Application Control Center, Attention: (CFDA #), Room 3633, Regional Office Building #3, 7th & D Streets, SW., Washington, DC 20202

Instructions for Application for Federal Assistance (Nonconstruction Programs)

Introduction

The instructions which follow should be followed by all applicants in completing applications for all NIDRR research and demonstration grants.

SF 424 and Parts II, III, IVa, and V are to be used for new applications.

SF 424 and Parts II, III, IVb, and V are to be used for the usual noncompeting continuation requests.

Submit the original and two copies of the form. If an item cannot be answered or does not appear to be related or relevant to the assistance required, write "NA" for not applicable.

Submission of Applications

(1) Continuation Grants—Applicants for continuation grants must submit these forms not later than 90 days prior to the budget period end date.

(2) New Projects—Applicants for grants to support new projects should refer to program announcements for information regarding deadline dates for submission of forms.

Supplemental Instructions for Completion of Part I (SF 424)

Part I of this application consists of the standard face page for Federal applications, the standard instructions for the face page, and these supplemental instructions.

Applicant shall complete all items. If an item is not applicable, write "NA." If additional space is needed, insert an asterisk (*) and use the remarks section.

Item

1. Preprinted.

3a–b. Not applicable.

4a–4h. If the payee will be other than the applicant, enter in the remarks section "payee," the payee's name, department or division, complete address and employer identification number or ED entity number.

If an individual's name and/or title is desired on the payment instrument, the name and/or title of the designated individual must be specified.

6a. Preprinted.

6b. Enter specific program identifier; for example, Research and Training Center, Rehabilitation Engineering Center, Research and Demonstration, or Utilization and Dissemination.

11. Preprinted.

19. Preprinted.

Supplemental Instructions for Completion of Part II

Item 1—On the same page show the Catalog of Federal Domestic Assistance number, the program number, the type of assistance, the status, the amount of each project where there is related previous, pending, or anticipated assistance from another source.

Supplemental Instructions for Completion of Part III

This form is designed so that application can be made for funds to support one or more functions or activities. Generally, NIDRR funded programs do not require a breakdown by function or activity. Therefore, only Line 1 need be completed.

Since NIDRR programs award funds to support activities for budget periods which are generally 12 months in duration, Section A, B, C, and D must provide budget information for the requested budget period. Section E should present the need for Federal assistance in subsequent budget periods.

Applicants for research grants are not required to complete information items related to non-Federal share. Rather, research cost sharing shall be negotiated separately with the funding office.

Section A–Budget Summary

Lines 1–4

Col. (a): Applicants may, at their discretion, present budget information for Section A (and Section B) in terms of major functions or activities. For example, common categories might be research and demonstration, dissemination, evaluation, or training.

Applicants who choose not to present budget information in terms of major functions and/or activities should enter Rehab. R&D on Line 1, Column (a) and note N/A on Lines 2–4.

Col. (b): Preprinted.

Col. (c)–(g): For *new applications,* leave Columns (c) and (d) blank. For each line entry, enter in Columns (e), (f), and (g) the appropriate amounts needed to support the project for the first budget period. Applicants for research grants should make *no* entries in Column (f).

For *continuation applications,* enter in Columns (c) and (d) the estimated amounts for funds which will remain unobligated at the end of the current budget period. Enter in Columns (e), (f), and (g) the appropriate amounts needed to support the project for the new budget period. (Applicants for research grants should make no entries in Column (d) or (f). Column (g) should equal the total of Column (e) and Column (f).)

For *changes to existing grants,* leave Columns (c) and (d) blank and enter in Columns (e) and (f) the amount of increase or decrease of Federal and non-Federal funds, as appropriate. Enter in Column g the new total budgeted amount (Federal and non-Federal) which includes the previously authorized total budgeted amounts for the current budget period plus or minus, as appropriate, the amounts shown in Columns (e) and (f). *The amount(s) in Column (g) should not equal the sum of the amounts in Column (e) and (f).* Applicants for research grants should make *no* entries in Column (d) or (f).

Line 5

Enter the totals for all columns completed.

Section B—Budget Categories

Columns 1–5

In the Column headings (1) through (4), enter the same title of the grant programs shown on Lines 1 through 4, Column (a), Section A. For each grant program or activity entered in Columns (1) through (4), enter the total requirements for *Federal funds* by object class categories and enter total in Column 5.

Allowability of costs are governed by applicable cost principles set forth in Subpart Q of 34 CFR Part 74.

Line 6a: Enter the total costs of salaries and wages of applicant/grantee staff. Do not include costs of consultants. (See Section F, Line 21, for additional requirements.)

Line 6b: Enter the total costs of fringe benefits unless treated as part of an approved indirect cost rate.

Line 6c: Enter total costs of *out-of-town* travel for employees of the project. Do not enter costs for consultant's travel or local transportation. (See Line 6h and Section F, Line 21, for additional instructions.)

Line 6d: Enter the total costs of all non-expendable personal property to be acquired by the project. "Non-expendable personal property" means tangible personal property having a useful life of more than one year and an acquisition cost of $300 or more per unit. An applicant may use its own definition of non-expendable personal property, provided that such a definition would be at least include all tangible personal property as defined in the preceding sentence. (See Section F, Line 21, for additional requirements.)

Line 6e: Enter the total costs of all tangible personal property (supplies) other than that included on Line 6d.

Line 6f: Enter the total costs of all contracts, including (1) procurement contracts (except those which belong on other lines, such as equipment, supplies, etc.), and (2) contracts with secondary recipient organizations. Also include any contracts with *organizations* for the provisions of technical assistance. Do *not* include payments to individuals on this line. Attach a list of contractors, indicating the name of the organization, the purpose of the contract and the estimated dollar amount of award. (*Note*: Whenever the applicant/grantee intends to delegate part or all of the program to another agency, the applicant/grantee must submit Sections A and B of Part III, Budget Section,

completed for each delegate agency by agency title, along with the required supporting information referenced in the applicable instructions. The total costs of all such agencies will be part of the amount shown on Line 6(f).)

Line 6g: Enter the costs of renovation or repair. *New construction is unallowable.*

Line 6h: Enter the total of all other costs. Such costs, where applicable, may include, but are not limited to, insurance, fees and travel paid directly to individual consultants, local transportation (all travel which does not require per diem is considered local travel), space and equipment rentals, printing and publication, computer use, training costs, including tuition and stipends, training service costs, including wage payments to individuals and supportive service payments, and staff development costs.

Line 6i: Show the totals of Lines 6(a) through 6(h).

Line 6j: Enter the total amount of indicated costs. If no indirect costs are requested, enter "none." This line should be used only when the applicant (except local governments) has an indirect cost rate approved by the Department of Education. Local governments shall enter the amount of indirect costs determined in accordance with ED requirements.

Line 6k: Enter the total amounts of Lines 6(i) and 6(j). For all new and continuation applications and total amount shown in Column (5), Line 6(k), should be the same as the amount shown in Section A, Column (e), Line 5.

For all changes, the total of the amount shown in Columns (1) through (4) should equal the amount shown in Section A, Line 5(e). The amount shown in Column (5) should include the cumulative total of the previously approved Federal share for the current budget period plus or minus, as appropriate, the increase or decrease of Federal funds.

Line 7: Enter the estimated amount of income, if any, expected to be generated from this project. Do not add or subtract this amount from the total project amount. Show, in the program narrative statement, the nature and source of income.

Section C—Non-Federal Resources

Line 8: Enter amounts of non-Federal resources that will be used to support the project. (Applicants for research grants should not complete this Section but will negotiate appropriate cost sharing arrangements with the funding office.) Provide a brief explanation, on a separate sheet, showing the type of contribution, and whether it is in cash or in kind. If in kind is allowable and included, show the basis for computation including:

(1) Numbers and types of volunteers and rates at which their services are valued;

(2) Valuation of donated space (use only) including number of square feet and value assigned per square foot; and

(3) Determination of depreciation and use allowance for grantee-owned space;

(4) Type and value of other in kind contributions expected.

Column (a): Enter the program title or activities as in Column (a), Section A.

Column (b): Enter the amount of cash and in kind contributions to be made by the applicant.

Column (c): Enter the State contribution. If the applicant is a State agency, enter the non-Federal funds to be contributed by the State other than the applicant State Agency.

Column (d): Enter the amount of cash and in kind contributions to be made from all other sources.

Column (e): Enter the totals of Columns, (b), (c), and (d).

Section E—Budget Estimates of Federal Funds Needed for Balance of Project

Line 9: Enter in Column (a) the same program title or activities as in Column (a), Section A. For new applications and continuation grant applications, enter in the proper columns amounts of Federal funds which will be needed to complete the program or project over the succeeding budget periods (usually in years). This Section need not be completed for revisions or supplements for the current budget period which do not increase the general level of support.

Section F—Other Budget Information

Line 10: Use this space to fully explain and justify the major items included in the budget categories shown in section B. Include sufficient detail to facilitate determination of allowability, relevance to the project, and cost benefits. Particular attention must be given to the explanation of any requested direct cost budget item which requires explicit approval by the program office. Budget items which require identification and justification shall include, but not be limited to, the following:

1. Salary amounts and percentage of time worked for project staff;

2. Out-of-town and foreign travel;

3. A list of all equipment to be purchased wholly or in part with grant funds which meets the definition of nonexpendable personal property provided on Line 6d, Section B;

4. Consultants: Fees, per diem, and travel;

5. Contractual; Major items or groups of smaller items; and

6. Other: Group and major categories; e.g., local transportation, space rental, training allowances, staff training, etc.

Line 11: Enter the type of indirect rate (provisional, pre-determined, final or fixed) that will be in effect during the funding period, the estimated amount of the base to which the rate is applied and the total indirect expense. Also, enter the date ED approved the rate, where applicable.

Line 12: Provide any other explanations required or deemed necessary.

BILLING CODE 4000-01-M

OMB Approval No. 0348-0006

FEDERAL ASSISTANCE

1. TYPE OF SUBMISSION (Mark appropriate box)
- ☐ NOTICE OF INTENT (OPTIONAL)
- ☐ PREAPPLICATION
- ☒ APPLICATION

2. APPLICANT'S APPLICATION IDENTIFIER
- a. NUMBER
- b. DATE (Year month day) 19

3. STATE APPLICATION IDENTIFIER (NOTE: TO BE ASSIGNED BY STATE)
- a. NUMBER N/A
- b. DATE ASSIGNED (Year month day) N/A 19

Leave Blank

SECTION I—APPLICANT/RECIPIENT DATA

4. LEGAL APPLICANT/RECIPIENT
- a. Applicant Name
- b. Organization Unit
- c. Street/P.O. Box
- d. City
- e. County
- f. State
- g. ZIP Code.
- h. Contact Person (Name & Telephone No.)

5. EMPLOYER IDENTIFICATION NUMBER (EIN)

6. PROGRAM (From CFDA)
- a. NUMBER 84.133
- MULTIPLE ☐
- b. TITLE Rehabilitation Research

7. TITLE OF APPLICANT'S PROJECT (Use section IV of this form to provide a summary description of the project.)

8. TYPE OF APPLICANT/RECIPIENT
A—State; B—Interstate; C—Substate Organization; D—County; E—City; F—School District; G—Special Purpose District; H—Community Action Agency; I—Higher Educational Institution; J—Indian Tribe; K—Other (Specify):
Enter appropriate letter ☐

9. AREA OF PROJECT IMPACT (Names of cities, counties, states, etc.)

10. ESTIMATED NUMBER OF PERSONS BENEFITING

11. TYPE OF ASSISTANCE
A—Basic Grant; B—Supplemental Grant; C—Loan; D—Insurance; E—Other
Enter appropriate letter(s) A

12. PROPOSED FUNDING

a. FEDERAL	$	.00
b. APPLICANT		.00
c. STATE		.00
d. LOCAL		.00
e. OTHER		.00
f. Total	$	.00

13. CONGRESSIONAL DISTRICTS OF:
- a. APPLICANT
- b. PROJECT

15. PROJECT START DATE (Year month day) 19

16. PROJECT DURATION Months

18. DATE DUE TO FEDERAL AGENCY ► (Year month day) 19

14. TYPE OF APPLICATION
A—New; B—Renewal; C—Revision; D—Continuation; E—Augmentation
Enter appropriate letter A

17. TYPE OF CHANGE (For 14c or 14e)
A—Increase Dollars; B—Decrease Dollars; C—Increase Duration; D—Decrease Duration; E—Cancellation; F—Other (Specify):
Enter appropriate letter(s)

19. FEDERAL AGENCY TO RECEIVE REQUEST ► U.S. Department of Education, Application Control Center, Washington, DC
- a. ORGANIZATIONAL UNIT (IF APPROPRIATE)
- b. ADMINISTRATIVE CONTACT (IF KNOWN)
- c. ADDRESS

20. EXISTING FEDERAL GRANT IDENTIFICATION NUMBER

21. REMARKS ADDED ☐ Yes ☐ No

SECTION II—CERTIFICATION

22. THE APPLICANT CERTIFIES THAT ► To the best of my knowledge and belief, data in this preapplication/application are true and correct, the document has been duly authorized by the governing body of the applicant and the applicant will comply with the attached assurances if the assistance is approved.
- a. YES, THIS NOTICE OF INTENT/PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON: DATE _____
- b. NO, PROGRAM IS NOT COVERED BY E.O. 12372 ☐ OR PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW ☐

23. CERTIFYING REPRESENTATIVE
- a. TYPED NAME AND TITLE
- b. SIGNATURE

SECTION III—FEDERAL AGENCY ACTION

24. APPLICATION RECEIVED (Year month day) 19

25. FEDERAL APPLICATION IDENTIFICATION NUMBER

26. FEDERAL GRANT IDENTIFICATION

27. ACTION TAKEN
- ☐ a. AWARDED
- ☐ b. REJECTED
- ☐ c. RETURNED FOR AMENDMENT
- ☐ d. RETURNED FOR E.O. 12372 SUBMISSION BY APPLICANT TO STATE
- ☐ e. DEFERRED
- ☐ f. WITHDRAWN

28. FUNDING

a. FEDERAL	$	.00
b. APPLICANT		.00
c. STATE		.00
d. LOCAL		.00
e. OTHER		.00
f. TOTAL	$	.00

29. ACTION DATE ► (Year month day) 19

30. STARTING DATE (Year month date) 19

31. CONTACT FOR ADDITIONAL INFORMATION (Name and telephone number)

32. ENDING DATE (Year month date) 19

33. REMARKS ADDED ☐ Yes ☐ No

NSN 7540-01-008-8162
PREVIOUS EDITION IS NOT USABLE

424-103

STANDARD FORM 424 PAGE 1 (Rev. 4-84)
Prescribed by OMB Circular A-102

BILLING CODE 4000-01-C

Part II Project, Approval Information

Item 1

Is there related assistance on this project previous, pending or anticipated? ☐ Yes

See instructions for additional information to be provided. ☐ No

BILLING CODE 4000-01-M

OMB Approval No. 0348-0044

BUDGET INFORMATION — Non-Construction Programs

SECTION A – BUDGET SUMMARY

Grant Program Function or Activity (a)	Catalog of Federal Domestic Assistance Number (b)	Estimated Unobligated Funds		New or Revised Budget		
		Federal (c)	Non-Federal (d)	Federal (e)	Non-Federal (f)	Total (g)
1.		$	$	$	$	$
2.						
3.						
4.						
5. TOTALS		$	$	$	$	$

SECTION B – BUDGET CATEGORIES

6 Object Class Categories	GRANT PROGRAM, FUNCTION OR ACTIVITY				Total (5)
	(1)	(2)	(3)	(4)	
a. Personnel	$	$	$	$	$
b. Fringe Benefits					
c. Travel					
d. Equipment					
e. Supplies					
f. Contractual					
g. Construction					
h. Other					
i. Total Direct Charges (sum of 6a - 6h)					
j. Indirect Charges					
k. TOTALS (sum of 6i and 6j)	$	$	$	$	$
7. Program Income	$	$	$	$	$

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SECTION C - NON-FEDERAL RESOURCES

(a) Grant Program	(b) Applicant	(c) State	(d) Other Sources	(e) TOTALS
8.	$	$	$	$
9.				
10.				
11.				
12. **TOTALS** (sum of lines 8 and 11)	$	$	$	$

SECTION E - BUDGET ESTIMATES OF FEDERAL FUNDS NEEDED FOR BALANCE OF THE PROJECT

(a) Grant Program	FUTURE FUNDING PERIODS (Years)			
	(b) First	(c) Second	(d) Third	(e) Fourth
16.	$	$	$	$
17.				
18.				
19.				
20. **TOTALS** (sum of lines 16 -19)	$	$	$	$

SECTION F - OTHER BUDGET INFORMATION

(Attach additional Sheets if Necessary)

21. Direct Charges:	22. Indirect Charges:
23. Remarks	

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Instructions for Completion of Part IV—Project Narrative for New and Continuation Applications

NIDRR recommends that the narrative section include the basic information described below and that applicants limit their applications according to the following guidelines:

- 100 pages for applications for Rehabilitation Research and Training Centers, Rehabilitation Engineering Centers, and Special Projects and Demonstrations for Spinal Cord Injury.
- 40 pages for applications under the Research and Demonstration Projects, Knowledge Dissemination and Utilization Projets, Field-Initiated Research Projects, and Research Training and Career Development Projects.
- 20 pages for applications under the Innovation Grants program.
- 12 pages, which is the regulatory limit, for applications under the Fellowship Program.

Should the proposed project be funded, the information provided in the "project narrative" will form the basis for evaluating progress for continuation funding.

The narrative for new applications may be organized under the major headings of the selection criteria included in the regulations governing the specific programs. These selection criteria are included in this Consolidated Application Package.

BILLING CODE 4000-01-M

OMB Approval No. 0348-0040

ASSURANCES — NON-CONSTRUCTION PROGRAMS

Note: Certain of these assurances may not be applicable to your project or program. If you have questions, please contact the awarding agency. Further, certain Federal awarding agencies may require applicants to certify to additional assurances. If such is the case, you will be notified.

As the duly authorized representative of the applicant I certify that the applicant:

1. Has the legal authority to apply for Federal assistance, and the institutional, managerial and financial capability (including funds sufficient to pay the non-Federal share of project costs) to ensure proper planning, management and completion of the project described in this application.
2. Will give the awarding agency, the Comptroller General of the United States, and if appropriate, the State, through any authorized representative, access to and the right to examine all records, books, papers, or documents related to the award; and will establish a proper accounting system in accordance with generally accepted accounting standards or agency directives.
3. Will establish safeguards to prohibit employees from using their positions for a purpose that constitutes or presents the appearance of personal or organizational conflict of interest, or personal gain.
4. Will initiate and complete the work within the applicable time frame after receipt of approval of the awarding agency.
5. Will comply with the Intergovernmental Personnel Act of 1970 (42 U.S.C. §§ 4728-4763) relating to prescribed standards for merit systems for programs funded under one of the nineteen statutes or regulations specified in Appendix A of OPM's Standards for a Merit System of Personnel Administration (5 C.F.R. 900, Subpart F).
6. Will comply with all Federal statutes relating to nondiscrimination. These include but are not limited to: (a) Title VI of the Civil Rights Act of 1964 (P.L. 88-352) which prohibits discrimination on the basis of race, color or national origin; (b) Title IX of the Education Amendments of 1972, as amended (20 U.S.C. §§ 1681-1683, and 1685-1686), which prohibits discrimination on the basis of sex; (c) Section 504 of the Rehabilitation Act of 1973, as amended (29 U.S.C. § 794), which prohibits discrimination on the basis of handicaps; (d) the Age Discrimination Act of 1975, as amended (42 U.S.C.§§ 6101-6107), which prohibits discrimination on the basis of age; (e) the Drug Abuse Office and Treatment Act of 1972 (P.L. 92-255), as amended, relating to nondiscrimination on the basis of drug abuse; (f) the Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment and Rehabilitation Act of 1970 (P.L. 91-616), as amended, relating to nondiscrimination on the basis of alcohol abuse or alcoholism; (g) §§ 523 and 527 of the Public Health Service Act of 1912 (42 U.S.C. 290 dd-3 and 290 ee-3), as amended, relating to confidentiality of alcohol and drug abuse patient records; (h) Title VIII of the Civil Rights Act of 1968 (42 U.S.C. § 3601 et seq.), as amended, relating to nondiscrimination in the sale, rental or financing of housing; (i) any other nondiscrimination provisions in the specific statute(s) under which application for Federal assistance is being made; and (j) the requirements of any other nondiscrimination statute(s) which may apply to the application.
7. Will comply, or has already complied, with the requirements of Titles II and III of the Uniform Relocation Assistance and Real Property Acquisition Policies Act of 1970 (P.L. 91-646) which provide for fair and equitable treatment of persons displaced or whose property is acquired as a result of Federal or federally assisted programs. These requirements apply to all interests in real property acquired for project purposes regardless of Federal participation in purchases.
8. Will comply with the provisions of the Hatch Act (5 U.S.C. §§ 1501-1508 and 7324-7328) which limit the political activities of employees whose principal employment activities are funded in whole or in part with Federal funds.
9. Will comply, as applicable, with the provisions of the Davis-Bacon Act (40 U.S.C. §§ 276a to 276a-7), the Copeland Act (40 U.S.C. § 276c and 18 U.S.C. §§ 874), and the Contract Work Hours and Safety Standards Act (40 U.S.C. §§ 327-333), regarding labor standards for federally assisted construction subagreements.

10. Will comply, if applicable, with flood insurance purchase requirements of Section 102(a) of the Flood Disaster Protection Act of 1973 (P.L. 93-234) which requires recipients in a special flood hazard area to participate in the program andto purchase flood insurance if the total cost of insurable construction and acquisition is $10,000 or more.

11. Will comply with environmental standards which may be prescribed pursuant to the following: (a) institution of environmental quality control measures under the National Environmental Policy Act of 1969 (P.L. 91-190) and Executive Order (EO) 11514; (b) notification of violating facilities pursuant to EO 11738; (c) protection of wetlands pursuant to EO 11990; (d) evaluation of flood hazards in floodplains in accordance with EO 11988; (e) assurance of project consistency with the approved State management program developed under the Coastal Zone Management Act of 1972 (16 U.S.C. §§ 1451 et seq.); (f) conformity of Federal actions to State (Clear Air) Implementation Plans under Section 176(c) of the Clear Air Act of 1955, as amended (42 U.S.C. § 7401 et seq.); (g) protection of underground sources of drinking water under the Safe Drinking Water Act of 1974, as amended, (P.L. 93-523); and (h) protection of endangered species under the Endangered Species Act of 1973, as amended, (P.L. 93-205).

12. Will comply with the Wild and Scenic Rivers Act of 1968 (16 U.S.C. §§ 1271 et seq.) related to protecting components or potential components of the national wild and scenic rivers system.

13. Will assist the awarding agency in assuring compliance with Section 106 of the National Historic Preservation Act of 1966, as amended (16 U.S.C. 470), EO 11593 (identification and protection of historic properties), and the Archaeological and Historic Preservation Act of 1974 (16 U.S.C. 469a-1 et seq.).

14. Will comply with P.L. 93-348 regarding the protection of human subjects involved in research, development, and related activities supported by this award of assistance.

15. Will comply with the Laboratory Animal Welfare Act of 1966 (P.L. 89-544, as amended, 7 U.S.C. 2131 et seq.) pertaining to the care, handling, and treatment of warm blooded animals held for research, teaching, or other activities supported by this award of assistance.

16. Will comply with the Lead-Based Paint Poisoning Prevention Act (42 U.S.C. §§ 4801 et seq.) which prohibits the use of lead based paint in construction or rehabilitation of residence structures.

17. Will cause to be performed the required financial and compliance audits in accordance with the Single Audit Act of 1984.

18. Will comply with all applicable requirements of all other Federal laws, executive orders, regulations and policies governing this program.

SIGNATURE OF AUTHORIZED CERTIFYING OFFICIAL	TITLE
APPLICANT ORGANIZATION	DATE SUBMITTED

SF 424B (4-88) Back

IMPORTANT NOTICE TO PROSPECTIVE PARTICIPANTS IN USDE CONTRACT AND GRANT PROGRAMS

GRANTS

Applicants for grants from the U.S. Department of Education (USDE) have to compete for limited funds.

Deadlines assure all applicants that they will be treated fairly and equally, without last minute haste.

For these reasons, USDE must set strict deadlines for grant applications. Prospective applicants can avoid disappointment if they understand that –

Failure to meet a deadline will mean that an application will be rejected without any consideration whatever.

The rules, including the deadline, for applying for each grant are published, individually, in the Federal Register. A one-year subscription to the Register may be obtained by sending $300.00 to: Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402-9371. (Send check or money order only, no cash or stamps.)

The instructions in the Federal Register must be followed exactly. Do not accept any other advice you may receive. No USDE employee is authorized to extend any deadline published in the Register.

Questions regarding submission of applications may be addressed to:

U.S. Department of Education
Application Control Center
Washington, D.C. 20202

CONTRACTS

Competitive procurement actions undertaken by the USDE are governed by the Federal Procurement Regulations and implementing ED Procurement Regulations.

Generally, prospective competitive procurement actions are synopsized in the Commerce Business Daily (CBD). Prospective offerors are therein advised of the nature of the procurement and where to apply for copies of the Request for Proposals.

Offerors are advised to be guided solely by the contents of the CBD synopsis and the instructions contained in the Request for Proposals (RFP). Questions regarding the submission of offers should be addressed to the Contracting Officer identified on the face page of the RFP.

Offers are judged in competition with others, and failure to conform with any substantive requirements of the RFP will result in rejection of the offer without any consideration whatever.

Do not accept any advice you receive that is contrary to instructions contained in either the CBD synopsis or the RFP. No USDE employee is authorized to consider a proposal which is non-responsive to the RFP.

A subscription to the CBD is available for $173.00 per year via non-priority mail or $243.00 per year via priority mail. Information included in the Federal Acquisition Regulations is contained in Title 48, Code of Federal Regulations, Chapter 1 ($90.00). The foregoing publication may be obtained by sending your check or money order only, no cash or stamps, to:

Superintendent of Documents
U.S. Government Printing Office
Washington, D.C. 20402-9371

In an effort to be certain this important information is widely disseminated, this notice is being included in all USDE mail to the public. You may, therefore, receive more than one notice. If you do, we apologize for any annoyance it may cause you.

ED FORM 5348, 6/88 REPLACES ED FORM 5348, 5/84, WHICH IS OBSOLETE

[FR Doc. 88-20104 Filed 9-7-88; 8:45 am]
BILLING CODE 4000-01-C

federal register

Thursday,
September 8, 1988

Part IV

Department of Health and Human Services

Health Care Financing Administration

Medicare Program; Withdrawal of Coverage of Single Photon Absorptiometry and Radiographic Absorptiometry and Radiographic Absorptiometry (Photodensitometry) and Continued Noncoverage of Dual Photon Absorptiometry; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

[BERC-446-PN]

Medicare Program, Withdrawal of Coverage of Single Photon Absorptiometry and Radiographic Absorptiometry (Photodensitometry) and Continued Noncoverage of Dual Photon Absorptiometry

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Proposed notice.

SUMMARY: This notice announces the Medicare program's intent to withdraw Medicare coverage (including coverage under the End Stage Renal Disease (ESRD) program) for single photon absorptiometry, and radiographic absorptiometry (photodensitometry) for measuring bone mineral density for either diagnostic purposes or as a guide to treatment, and to continue noncoverage of dual photon absorptiometry.

DATE: Comments will be considered if we receive them at the appropriate address, as provided below, no later than 5:00 p.m. on November 7, 1988.

ADDRESS: Mail comments to the following address: Health Care Financing Administration, Department of Health and Human Services, Attention: BERC-446-PN, P.O. Box 26676, Baltimore, Maryland 21207.

If you prefer, you may deliver your comments to one of the following addresses:

Room 309-G, Hubert H. Humphrey Building, 200 Independence Ave., SW., Washington, DC, or

Room 132, East High Rise Building, 6325 Security Boulevard, Baltimore, Maryland.

In commenting, please refer to file code BERC-446-PN. Comments received timely will be available for public inspection as they are received, generally beginning approximately three weeks after publication of a document, in Room 309-G of the Department's offices at 200 Independence Ave., SW., Washington, DC, Monday through Friday of each week from 8:30 a.m. to 5:00 p.m. (phone: 202-245-7890).

FOR FURTHER INFORMATION CONTACT: Barton McCann, M.D., (301) 594-9370.

SUPPLEMENTARY INFORMATION:

I. Background

Administration of the Medicare program is governed by the Medicare statute, title XVIII of the Social Security Act (the Act). The Medicare law provides coverage for broad categories of benefits, including inpatient and outpatient hospital care, skilled nursing facility (SNF) care, home health care, and physicians' services. It places general and categorical limitations on the coverage of the services furnished by certain health care practitioners, such as dentists, chiropractors and podiatrists, and it specifically excludes some categories of services from coverage, such as cosmetic surgery, personal comfort items, custodial care, routine physical checkups, and procedures that are not reasonable and necessary for diagnosis or treatment. The statute also provides direction as to the manner in which payment is made for Medicare services, the rules governing eligibility for services, and the health, safety and quality standards to be met by institutions providing services to Medicare beneficiaries.

The Medicare law does not, however, provide an all-inclusive list of specific items, services, treatments, procedures, or technologies covered by Medicare. Thus, except for the examples of durable medical equipment in section 1861(n) of the Act, and some of the medical and other health services listed in sections 1861(s) and 1862(a) of the Act, the statute does not specify medical devices, surgical procedures, or diagnostic or therapeutic services that should be covered or excluded from coverage.

The intention of Congress, at the time the Medicare Act was enacted in 1965, was that Medicare would provide health insurance to protect the elderly or disabled from the substantial costs of acute health care services, principally hospital care. The provision was designed generally to cover services ordinarily furnished by hospitals, SNFs, and physicians licensed to practice medicine. Congress understood that questions as to coverage of specific services would invariably arise and would require a specific decision of coverage by those administering the program. Thus, it vested in the Secretary the authority to make those decisions. Specifically, section 1862(a)(1)(A) of the Act prohibits payment for any expenses incurred for items or services "which are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."

We have interpreted this statutory provision to exclude from Medicare coverage those medical and health care services that are not demonstrated to be safe and effective by acceptable clinical evidence. Effectiveness in this context is defined as the probability of benefit to individuals from a medical technology for a given medical problem under actual conditions of use. In day-to-day medical practice, physicians diagnose and treat clinical conditions following their performance of history and physical examinations and their interpretations of a variety of diagnostic tests and procedures. To be of value to the physician in confirming the presence or absence of a given disease, the information obtained from any diagnostic test or procedure must be of sufficient accuracy to establish or rule out the presence of that disease. Likewise, for established diagnoses, the test or procedure must be of sufficient precision to allow the physician to accurately monitor the patient's response to treatment. Payment may not be made under Medicare for any diagnostic test or procedure that is not accurate or precise, since such a test cannot be considered "reasonable and necessary for the diagnosis or treatment of illness or injury". While medical procedures may prove to be efficacious in a research setting, under ideal circumstances (that is, controlled environment, scientifically trained users, optimally functioning equipment, etc.) their efficacy may not extend to less controlled settings. On April 29, 1987, we published a notice in the Federal Register (52 FR 15560) that describes the process we use in reaching coverage decisions. That notice includes a discussion of our reliance on the Office of Health Technology Assessment (OHTA) in the Public Health Service (PHS) for medical advice.

The Medicare program currently covers single photon absorptiometry, radiographic absorptiometry (photodensitometry), and bone biopsy for measuring bone mineral density. Dual photon absorptiometry currently is not covered.

Bone mineral density studies are used to diagnose diseases of the bone and to evaluate the responses of bone diseases to treatment. The studies assess bone mass or density associated with such diseases as osteoporosis, osteomalacia, and renal osteodystrophy. Various methods of measurement may be used to diagnose bone disease and monitor the response to treatment, including, bone biopsy, radiographic absorptiometry (photodensitometry), and single and dual photon absorptiometry.

A bone biopsy is an invasive surgical procedure. A small sample of bone (usually from the hip) is removed, generally by a biopsy needle. The biopsy sample is then examined histologically, and provides a qualitative measurement of the bone mineral

content of the trabecular bone. This procedure is used primarily to differentiate osteomalacia from osteoporosis. Bone biopsy is covered under Medicare when used for the qualitative evaluation of bone no more than four times per patient, unless special justification is given. When used more than four times on a patient, bone biopsy may leave a defect in the pelvis and produce some patient discomfort.

Radiographic absorptiometry (photodensitometry) is a noninvasive radiological procedure that attempts to assess bone mass by measuring the optical density of extremity radiographs with a photodensitometer, usually with a reference to a standard density wedge placed on the film at the time of exposure. This procedure provides a quantitative measurement of the bone mineral of cortical bone, and is used for monitoring gross bone change.

Radiographic absorptiometry (photodensitometry) was covered in 1975 at the recommendation of the Bureau of Health Insurance's (predecessor to HCFA) in-house medical consultants based on the limited medical information available at that time. This decision was made prior to the inception of the HCFA Physicians Panel and OHTA review and assessment process. Since that time additional studies have been conducted, with the result that the available evidence as set forth in current medical literature no longer supports Medicare's coverage position.

Single photon absorptiometry is a non-invasive radiological technique that measures absorption of a monochromatic photon beam by bone material. The device is placed directly on the patient, uses a low dose of radionuclide, and measures the mass absorption efficiency of the energy used. It provides a quantitative measurement of the bone mineral of cortical and trabecular bone, and is used in assessing an individual's treatment response at appropriate intervals. Single photon absorptiometry has been covered under Medicare when used in assessing changes in bone density of patients with osteodystrophy or osteoporosis when performed on the same individual at intervals of six to 12 months.

Single photon absorptiometry was covered under Medicare based on the advice and recommendation of the Office of Health Research, Statistics, and Technology (OHRST), PHS on September 10, 1982. OHRST stated that while no single currently available technique was entirely satisfactory for assessing either the degree or type of bone disease in individual patients, they recommended that single photon absorptiometry be covered under Medicare because "There does *appear* to be evidence to support the clinical effectiveness of photon absorptiometry * * *" Since that time additional studies have been conducted, with the result that the available evidence as set forth in current medical literature no longer supports Medicare's coverage position.

Dual photon absorptiometry is a noninvasive radiological technique that measures absorption of a dichromatic beam by bone material. This procedure is not covered under Medicare because it is still considered to be in the investigational stage.

The issue of the safety and effectiveness of dual photon absorptiometry was considered by the HCFA Physicians Panel on January 11, 1984. The HCFA Physicians Panel is an internal organization composed of physicians and other health professionals in HCFA's Central Office and their counterparts from PHS, which meets approximately once every six to eight weeks. At that time, the Panel recommended that HCFA refer the issue to PHS for its review with specific direction to OHTA to report back to HCFA after it had reviewed the data presented at a Consensus Conference on Osteoporosis at the National Institutes of Health (NIH) in April of 1984.

OHTA reported on the NIH conference at the Panel meeting held May 15, 1984. The NIH conference was unable to reach a consensus on the effectiveness in the clinical setting of any of the currently available tests for studying bone mineral density. The discussion generated by this information led HCFA to question whether these techniques were medically necessary, given the current state of therapy for osteoporosis. A major conclusion of the NIH conference was that while there are a number of promising treatments available for osteoporosis, there was no single treatment available to either prevent or cure the condition. The Panel then recommended that OHTA be requested to do a full assessment of the effectiveness of all types of bone mineral density studies.

On June 1, 1984, we requested that OHTA assess the issue of the safety and effectiveness of all currently used bone mineral density studies—radiographic absorptiometry (photodensitometry), single photon absorptiometry, dual photon absorptiometry, and computerized tomography (CT) scans. In a **Federal Register** notice published October 26, 1984, OHTA announced that it was coordinating an assessment of what is known of the safety, clinical effectiveness, and use of bone mineral density studies. During its assessment, OHTA solicited information and advice from other PHS components (such as the Food and Drug Administration and NIH), consulted directly with concerned medical specialty groups and professional organizations to determine whether a consensus exists within the medical community concerning the safety and effectiveness of bone mineral density studies, and researched and analyzed published medical and scientific literature and findings of all relevant studies and reports. On December 31, 1986, OHTA recommended that we not cover single photon absorptiometry under Medicare (including the ESRD program), and continue to deny Medicare coverage of dual photon absorptiometry. On September 22, 1987, OHTA recommended that we not cover radiographic absorptiometry (photodensitometry) under Medicare.

According to the OHTA assessment, the use of radiographic absorptiometry (photodensitometry), single photon absorptiometry, and dual photon absorptiometry for diagnosing bone loss or monitoring effectiveness of treatment is unproven. Currently, there is a lack of medical evidence supporting their effectiveness as either diagnostic tools or methods of monitoring treatments for bone disease when used outside the research setting. Because of significant variation among observers in obtaining measurements, and because measurements by the same observer at different times vary to a considerable degree, the accuracy of these measurements must be considered open to question. Moreover, it has not been determined which site or sites are best suited for measurement. When used as a guide to monitoring treatment response the degree of change in bone density expected is smaller than the precision error of the devices themselves, thereby making such measurements unsuitable for this purpose. OHTA has advised that radiographic absorptiometry (photodensitometry), single photon absorptiometry, and dual photon absorptiometry need to undergo further clinical investigation before being recommended for general clinical use. OHTA has, therefore, concluded that the available clinical and scientific evidence does not support the effectiveness in a day-to-day clinical setting, of radiographic absorptiometry (photodensitometry), single photon absorptiometry, and dual photon absorptiometry in measuring bone mineral density for either diagnostic or treatment monitoring purposes.

HCFA has received recently comments form clinicians and others challenging the OHTA assessments of the effectiveness of radiographic absorptiometry (photodensitometry), single photon absorptiometry, and dual photon absorptiometry in measuring bone mineral density for either diagnostic or treatment monitoring purposes that may have a substantial, credible basis. These comments will be available for public inspection during the comment period for this notice and will be addressed in the final notice if we proceed with publishing one.

OHTA is currently assessing the safety and effectiveness of computerized tomography (CT) scans when used to measure bone mineral density.

II. Provisions of the Proposed Notice

We propose to exclude radiographic absorptiometry (photodensitometry) and single photon absorptiometry for measuring bone mineral density from Medicare coverage (including coverage under the ESRD program) for either diagnostic purposes or as a guide to treatment, and to continue noncoverage of dual photon absorptiometry.

The provisions of this notice would not affect any existing Medicare regulations. However, they would affect the following manual instructions:

- Coverage Issues Manual—Section 50–17, paragraph A, Laboratory Tests—CRD Patients; and Section 50–44, Bone Mineral Density Studies;
- Renal Dialysis Facility Manual—Section 240.3, paragraph D, Laboratory Tests;
- Hospital Manual—Section 238.2, paragraph D.3., Institutional Dialysis Services Furnished to CAPD Patients—Laboratory Tests;
- Intermediary Manual—Section 3172.3, Laboratory Tests for Hemodialysis, Intermittent Pertioneal Dialysis (IPD) and Continuous Cycling Pertioneal Dialysis (CCPD) Included in the Composite Rate—Guidelines for Separately Billable Tests for Hemodialysis, IPD, and CCPD; and
- Carriers Manual—Section 2231.3, Support Services and Supplies Furnished to Home CAPD Patients, paragraph D.3., Laboratory Tests; and Section 4270, paragraph C.3., Guidelines for Separately Billable Tests for Hemodialysis, IPD, and CCPD.

III. Appendices

We have included as appendices to this notice the following OHTA assessments of single and dual photon absorptiometry.

APPENDIX I—Public Health Service Reassessment of Single Photon Absorptiometry for Measuring Bone Mineral Density—1986

APPENDIX II—Public Health Service Assessment of Dual Photon Absorptiometry for Measuring Bone Mineral Density—1986

APPENDIX III—Public Health Service Assessment of Radiographic Absorptiometry for Measuring Bone Mineral Density—1987

IV. Regulatory Impact Statement

Executive Order (E.O.) 12291 requires us to prepare and publish an initial regulatory impact analysis for any proposed notice that meets one of the E.O. criteria for a "major rule"; that is, that would be likely to result in: An annual effect on the economy of $100 million or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets. In addition, we generally prepare an initial regulatory flexibility analysis that is consistent with the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 through 612), unless the Secretary certifies that a proposed notice such as this would not have a significant economic impact on a substantial number of small entities.

Although radiographic absorptiometry has been covered since 1975, the first year for which Medicare coverage was available for single photon absorptiometry was 1985. The limited data available to us show the total 1985 Medicare charges for both procedures were significantly less than $1 million. This proposal would affect those clinics and other facilities that are offering this testing in two ways: first, they would lose Medicare revenue, and second, our coverage decision may affect other payers (such as, third parties) and their beneficiaries. Nonetheless, we believe the economic impact of this notice would not be significant.

For these reasons, we have determined that a regulatory impact analysis is not required. Further, we have determined and the Secretary certifies that this proposed notice would not have a significant economic impact on a substantial number of small entities, and we have therefore not prepared a regulatory flexibility analysis.

V. Response To Comments

Because of the large number of comments we receive on proposed notices, we cannot acknowledge or respond to them individually. However, in preparing the final notice, we will consider all comments received timely and respond to the major issues in that notice.

VI. Collection Of Information Requirements

This notice contains no information collection requirements. Consequently, this notice need not be reviewed by the Executive Office of Management and Budget under the authority of the Paperwork Reduction Act of 1980 (44 U.S.C. 3501 *et seq.*).

(Sec. 1862(a) of the Social Security Act (42 U.S.C. 1395y(a)))

(Catalog of Federal Domestic Assistance Program No. 13.773, Medicare Hospital Insurance and No. 13.774, Supplementary Medical Insurance)

Dated: February 26, 1988.

William L. Roper,

Administrator, Health Care Financing Administration.

Approved: April 9, 1988.

Otis R. Bowen,

Secretary.

BILLING CODE 4120-01-M

APPENDIX I - Public Health Service Reassessment of Single Photon Absorptiometry for Measuring Bone Mineral Density - 1986

Health Technology Assessment Reports, 1986

Single Photon Absorptiometry for Measuring Bone Mineral Density

Number 7



NATIONAL CENTER FOR HEALTH SERVICES RESEARCH AND HEALTH CARE TECHNOLOGY ASSESSMENT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

FOREWORD

The Office of Health Technology Assessment (OHTA) evaluates the safety and effectiveness of new or unestablished medical technologies that are being considered for coverage under Medicare. These assessments are performed at the request of the Health Care Financing Administration (HCFA). They are the basis for recommendations to HCFA regarding coverage policy decisions under Medicare.

Questions about Medicare coverage for certain health care technologies are directed to HCFA by such interested parties as insurers, manufacturers, Medicare contractors and practitioners. Those questions of a medical, scientific, or technical nature are formally referred to OHTA for assessment.

OHTA's assessment process includes a comprehensive review of the medical literature and emphasizes broad and open participation from within and outside the Federal Government. A range of expert advice is obtained by widely publicizing the plans for conducting the assessment through publication of an announcement in the Federal Register and solicitation of input from Federal agencies, medical specialty societies, insurers, and manufacturers. The involvement of these experts helps assure inclusion of the experienced and varying viewpoints needed to round out the data derived from individual scientific studies in the medical literature. After OHTA receives information from experts and the scientific literature, the results are analyzed and synthesized into an assessment report. Each report represents a detailed analysis of the safety, clinical effectiveness, and uses of new or unestablished medical technologies considered for Medicare coverage. These Health Technology Assessment Reports form the basis for the Public Health Service recommendations to HCFA and are disseminated widely.

Individual reports are available to the public once HCFA has made a coverage decision regarding the subject technology. OHTA also publishes compilations which contain all assessment reports submitted to HCFA in a given calendar year.

OHTA is part of the National Center for Health Services Research and Health Care Technology Assessment, Public Health Service, Department of Health and Human Services.

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PUBLIC HEALTH SERVICE REASSESSMENT SINGLE PHOTON ABSORPTIOMETRY FOR MEASURING BONE MINERAL DENSITY 1986

INTRODUCTION

Single photon absorptiometry (SPA) is a noninvasive radiologic technique used to assess bone mineral content in the appendicular skeleton (1). A photon beam from a sealed, single, low-energy radioisotope source is directed at a bone of the patient's limb, usually the shaft of the radius. As the beam passes through the bone and soft tissue, some photons are absorbed, and a nuclear counting instrument measures the intensity of the beam that emerges. The difference in photon absorption between bone and soft tissue allows for the calculation of the total bone mineral found in the scan path. The amount of skeletal mineral present is proportional to the change in beam intensity over the bone (2). The measurements by SPA are calibrated with known bone mineral content (BMC) from ashed bone sections or from standards calibrated against ashed bone sections. The SPA technique provides no information about the volume of bone scanned. In SPA, bone mineral is expressed in mass per unit length of bone (g/cm). Measurements of bone mineral by SPA have been used to provide an index of skeletal status in the assessment of a wide range of metabolic bone disorders such as renal osteodystrophy and osteoporosis.

First described in 1963, SPA is considered a simple, widely available, and relatively inexpensive bone mineral measurement technique (3). Initially, bones of the hands, humerus, femur, tibia, mandible, and calcaneus (os calcis or heel) were measured. Because of easy access to the forearm (radius) and better reproducibility, the

greatest experience has been collected with the forearm bones as scanning sites (1). Frequently used sites on the radius are the distal portion (10 percent of the total length from the styloid process of the ulna), distal third, and midradius. In current practice most radial bone measurements are limited to the midradius. For photon absorptiometry the midradius is a site two-thirds the length of the ulna from its proximal end. Some investigators also use measurements on ulna and radius together at the distal end of the radius (1). In the last 10 years, measurements of bone mineral in the forearms by SPA have become one of the most widely used methods for evaluating the cortical bone mass (4).

Recently, interest has centered on measurements of axial trabecular bone mass. Most nontraumatic fractures occur in the axial skeleton (spine) and proximal femur (hip), sites containing significant amounts of trabecular bone. Also, according to some investigators, bone mineral density (BMD) measurements made at the fracture sites (spine and hip) discriminate better between nontraumatic fragility fractures and nonfracture cases than measurements made on other parts of the skeleton (5,6). This has fueled a controversy regarding the value of radial appendicular (cortical) skeletal measurements for predicting the risk of developing a fracture at the spine or hip and monitoring the effects of therapy of osteoporosis. This recent interest in measurements of trabecular bone mass has also resulted in attempts to measure appendicular trabecular bone at the distal radius and os calcis. A major difficulty in measurements at these sites is the tapering bone and repositioning problem. Since the bone's cross section tapers sharply at the distal radius and is irregular at the os calcis, a small positioning change may produce a substantial change in bone diameter and measured BMD (5). According to Mazess, however, microcomputer-controlled instruments coupled to rectilinear scanners will greatly improve the precision of these instruments in sites where there is great variation in the bone cross section from one centimeter to another along the shaft of a

given bone (i.e., distal radius) (7). Rectilinear scanning of 1 cm segments of bone in 1 to 2 mm step-wise increments allows the averaging of multiple scans and improves precision.

SPA was first described by Cameron and Sorensen in 1963 (8). It was developed in an attempt to circumvent some of the problems inherent in the use of photodensitometry and radiogrammetry to measure BMD (8). The technique of SPA utilizes a well collimated beam of mono-energetic radiation, usually from I^{125} (200m Ci), to scan a peripheral bone (8). The absorption of photons is measured by a sodium iodide-thallium detector fixed on a C-frame opposite the photon source. This assembly synchronously scans across the bone being measured. Like radiogrammetry, SPA is limited to measurements of appendicular bone because tissue composition surrounding the bone has to be uniform and minimal. Corrections cannot be made by this instrument for bulk soft tissue or its uneven distribution around the bone. Because the technique requires a uniform soft tissue thickness surrounding the bone, the limb is immersed in water or wrapped with a water bag or tissue-equivalent material to simulate constant thickness in soft tissue (9).

Using SPA, the bone mineral measured reflects the total integrated mineral (cortical and trabecular) in the path of the beam. Calculations of bone mass in gm/cm are made with the use of standard curves. Standard curves are obtained by dividing an excised radius in pieces of 1-cm length and then scanning in the middle of these pieces. Scanning is performed under 4 cm of water. The 1-cm pieces are then ashed to constant weight. The calibration curve (standard curve) is obtained by plotting the ash weight of the dried, defatted human radius against the bone mineral as estimated with the SPA device (10). The units most frequently used with SPA are ash weight (in grams) per axial bone length (in centimeters).

SPA scans of the forearm take about 10 to 15 minutes and can be performed without specific preparation on most patients. According to Wahner, measurements of bone mineral with SPA are contraindicated in patients with skeletal abnormalities or history of fracture of the radius, recent immobilization of the arm, arthritic changes, or arteriovenous fistulas as used in renal dialysis (10). Costs for these devices range from about $19,000 to $25,000 (costs do not include radioactive source). The 200m Ci I^{125} radiation source that is required has a half life of 60 days. This source will have to be replaced every 4 to 5 months at a cost of about $750. Charges for the procedure range from about $50 to $150 (2). A comparison of SPA costs with those of other techniques for measuring bone mineral can be found in the costs section of the OHTA assessment for dual photon absorptiometry (DPA) (11).

Radiation exposure is always a concern with any procedure utilizing radiation sources. While SPA is a noninvasive technique, it does involve patient exposure to radiation. Wahner and colleagues have performed dosimetry measurements at the Mayo Clinic. They measured patient radiation dose from SPA of the radius utilizing I^{125} and four passes 1 mm apart. They found that the peak skin dose, with background measured at both eye and gonad sites, was 13 mrad (1).

According to the position paper on radiologic methods to evaluate BMC from the Health and Public Policy Committee of the American College of Physicians, SPA involves minimal radiation exposure, with negligible bone marrow or gonadal radiation (2). The position paper reports SPA involves a 2 to 5 mrad dose to the limb. The body dose is negligible as a result of little radiation scatter. Physicians are required to obtain the Nuclear Regulatory Commission Level VI license to handle the necessary 400 millicuries of I^{125} used in SPA (3).

The physiologic information provided by measurements of BMC have been under extensive investigation during the past 20 years. Bone mass measurements have been a valuable research tool for clinical investigations attempting to elucidate the

pathogenesis of metabolic bone diseases. Investigators have sought to determine the clinical significance of bone loss with aging and bone disease and its relationship to an increasing risk of fractures among the elderly. This growing interest in better understanding the nature and degree of changes in BMC with age, with osteoporosis, and with metabolic bone disease, in general, has prompted the development of noninvasive measurement techniques for assessing bone mineral content (12). A variety of such techniques in addition to SPA are presently available. They include: radiogrammetry, photodensitometry, radiographic absorptiometry, computed tomography, and DPA.

Although bone mineral measurements with SPA have been utilized mostly in studies of primary osteoporosis, a number of clinical investigations have been reported regarding its use in renal osteodystrophy (13,14,15,16,17). These studies which include work by Stewart and associates, Atkinson and colleagues and Griffiths and Zimmerman indicate that photon absorptiometry is suitable for epidemiological studies and clinical research in metabolic bone diseases associated with renal failure (13,14,17). However, the role of SPA measurements for individual case diagnosis and for patient management decisions is uncertain (6,14,16).

Many of the methods of bone mass quantitation in general, and SPA in particular, have been used in attempts to diagnose osteoporosis or to follow its response to therapy. This report will reassess the effectiveness of SPA bone mineral measurements on the clinical outcome of patients being evaluated and treated for osteopenic bone diseases. This reassessment seeks to ascertain where bone mineral evaluation by SPA fits into the overall scheme of osteoporosis prevention, diagnosis and treatment. A similar report has been published on DPA. The other noninvasive measurement techniques for bone mineral will be assessed subsequently, in separate reports.

BACKGROUND

Osteoporosis is a major public health problem. The National Institutes of Health Consensus Development Conference on Osteoporosis held on April 2-4, 1984, reported that osteoporosis may affect between 15 and 20 million Americans (18). More than 1 million fractures attributable to osteoporosis occur annually in individuals over the age of 45. Twenty-five percent of women over 60 years of age have documented vertebral fractures in association with osteoporosis. As many as 50 percent of women will develop vertebral fractures by age 75. These fractures may develop during routine activities, such as bending, lifting, or raising from a chair or bed (18). While compression fractures (collapsed fractures) of the vertebrae can produce severe pain, the amount of back pain and disability attributable to most vertebral fractures is unknown. According to the American College of Obstetricians and Gynecologists, after age 45 there is a marked increase in the incidence of distal forearm fractures (19). By age 60, there are 10 times more forearm fractures in women than in men of comparable age. These fractures limit the use of the extremity for 4 to 8 weeks, with long-term disability uncommon. While osteoporosis predisposes to fractures of various bones, hip fractures are the most serious in terms of disability, mortality and aggregate cost. In the United States, it is estimated that more than 200,000 hip fractures occur in elderly women each year with 80 percent found to be related to pre-existing osteoporosis (19). The affected population tends to be advanced in age and the sex distribution less skewed toward females than is the case with vertebral fractures. Acute complications such as depression and mechanical failure of the surgical procedure are common (18). Most patients fail to recover normal activity. Hip fractures lead to fatalities in 12 to 20 percent of cases and precipitate long-term nursing home care for half of those who survive (20,21). Hip fractures pose a significant economic as well as a medical burden.

The economic burden of all age-related fractures is great because of the large number of people involved and the expensive and protracted care that is often required. About a fourth of all patients with limb fractures require hospitalization and the mean hospital stay increases from 13.6 days among those age 25 to 44, to 32.6 days among those older than age 65. Fractures of the proximal femur account for more than half of all days of hospitalization for limb fractures. The cost of the acute care alone for fractures of the proximal femur has been estimated to exceed $1 billion annually in the United States (22). The direct and indirect costs of osteoporosis, including hip fractures, are estimated to be between $3.5 billion and $6.1 billion annually in the United States (18,21). As a result of the considerable morbidity, mortality and expenditures associated with this disease, there is growing interest in research regarding its prevention, diagnosis, and treatment. The pathogenesis of osteoporosis, its prevention and management has had extensive review. A summary of that information can be found in the osteoporosis section of the OHTA assessment on DPA (11). Additional information can also be obtained from the numerous references cited in that report.

For the past 5 years investigators have used SPA to assess the BMC of the appendicular skeleton in "normal" individuals and in patients with osteoporosis. Studies have been conducted to investigate whether appendicular (radial) bone mineral measurements could separate "normal" women from women with vertebral compression fractures or femoral neck fractures. Recently, some investigators have used SPA distal radial and os calcis measurements ostensibly to identify women at risk of future fractures. This report examines these and other studies as well as other evidence that pertains to the safety and clinical effectiveness of this technique.

RATIONALE

The rationale for bone mineral measurements in osteoporosis is based on the demonstration that the strength or resistance of a bone to fracture is closely related to the amount of bony tissue or the mass of the mineral present in the bone. Proponents argue that since the (breaking) tensile strength of bone mass is related to its mineral content, measurements of bone mineral should be a more accurate method of determining fracture risk. Proponents of SPA believe that the ability to assess the direction and degree of changes in bone mineral content in the os calcis, distal radial and midradial sites facilitates the diagnosis and management of metabolic bone diseases, such as osteoporosis. They argue that information on bone mineral loss is clinically important for the monitoring of age-related bone loss, for the diagnosis and monitoring of bone loss resulting from metabolic bone disease, for the assessment of drug effects on bone mineralization, and for the accurate assessment of fracture risk at the spine and femoral neck. Proponents also argue that these measurements could prove useful as clinical guides to therapy in assessing the therapeutic responses of patients with osteopenia.

REVIEW OF AVAILABLE INFORMATION

Accuracy and Precision

Accuracy defines the degree to which a measurement, or an estimate based on measurements, represents the true value of the attribute that is being measured. In this case it refers to how well the measurement reflects actual mineral content. It is expressed as a coefficient of variation (or error of estimate) of the difference between actual and measured. In the determination of osteopenia, accuracy in the measurement of bone mass by SPA is of great importance.

A number of complex technical factors affect absorptiometry accuracy determinations in vivo. These include beam hardening, photon beam size, scattered radiation and spatial variation of soft tissue composition (23). SPA minimizes the effects of scattered radiation and beam hardening that contribute to that inaccuracy. The narrow beam (less than 5mm diameter) eliminates problems of scattered radiation while use of nonenergetic radiation minimizes the effects of selective filtration of the beam as it passes through a limb (beam hardening) (23). According to Judy, the error introduced by hardening, scatter, and finite beam size can be reduced to less than 2 percent by calibrating the measurement system with an ash study (23).

Sorenson and Cameron, and Christiansen and coworkers have demonstrated that the mineral content of a bone as determined by SPA is independent of the position of the bone relative to top and bottom of the soft tissue and independent of the orientation of the bone in the soft tissue (24,25). It is also independent of a constant thickness of overlying tissue. However, the distribution of fat in the arm is such that its thickness, as seen by the scanning beam, is not uniform. Therefore, the accuracy of SPA is limited by the uncertainty and variation of soft tissue composition over and in the bone. The magnitude of this error has been estimated to be from 2 percent to as large as 30 percent (23). To minimize artifacts introduced by variation in soft tissue, the limb being studied is immersed in water or wrapped in a tissue-equivalent substance to simulate constant thickness.

The instrumental accuracy of SPA using I^{125} as the photon source was determined by Cameron and coworkers in 1968 (26). Excised bones were measured under water to simulate the soft tissue surrounding the limb and the mass of ashed sections was compared with the absorptiometric measurement. The authors reported accuracies of 4 to 7 percent for the SPA technique. With technical modifications (a rapid scanning automated system) made during the study, the authors demonstrated improved accuracies of 2 to 4 percent. More recently, Rustgi and colleagues found a 6.5 percent difference

when they compared measured BMC values obtained by SPA with absolute values obtained by the ashing method (27). In a 1983 review of noninvasive methods for quantitating appendicular bone mass, Johnston concluded that SPA provided an accurate assessment of the amount of mineral with an error of estimate of about 5 to 6 percent (9). Preliminary results from a study of bone mass in 50 postmenopausal osteoporotic women at the University of Washington was recently reported by Chestnut at the National Institutes of Health Consensus Development Conference on Osteoporosis (28). With SPA measurements of the radius/ulna, he reported obtaining an accuracy of 3 to 4 percent. Similar findings of accuracy (1-4 percent) have been reported in the position paper on radiologic methods to evaluate bone mineral content from the Health and Public Policy Committee of the American College of Physicians (2).

For monitoring changes in bone mass, SPA bone mineral measurements have to be sufficiently precise (reproducible) to provide a correct estimate of these changes. Precision is important if the goal is to detect small changes, such as the 1 to 2 percent per year loss of bone mass found in many postmenopausal women. The coefficient of variation (CV) expressed in percent describes the precision or reproducibility of a given measurement. A number of published studies have reported the precision of repeated SPA measurements to be between 2 and 4 percent (8,28,29).

Because accurate repositioning of the bone site for repeated measurements is the principal determinant of precision, a number of modifications to improve the repositioning error, including rectilinear scanning, have been introduced in different instruments. Using microcomputers, scans of multiple paths about 1 mm apart are feasible, giving an integrated bone mass over some distance (1). According to Mazess, rectilinear scanning can reduce the usual 2 to 4 percent error of linear scans to 1 to 2 percent (7). Similar results, under strictly controlled conditions, have been reported by

Wahner and coworkers (1). Johnston has found the precision of repeated SPA measurements quite good: 1 to 2 percent in the research laboratory, and 2 to 5 percent in the clinical setting (9).

Clinical Applications

One of the earliest studies of bone demineralization, using SPA measurements, was performed by Smith and associates on 169 white women older than 50 years of age at Indiana University School of Medicine in 1972 (29). They measured bone mineral at two radial sites in 56 women with and 113 women without fractured vertebrae. Although measurements of bone mineral in the radius were significantly less in the group with collapsed vertebrae, the authors reported considerable overlap in measurement values for the fracture and nonfracture groups (29). Because there appeared to be a greater loss of bone mineral from the radial site (one-tenth of the forearm length from the distal radius) containing higher percentages of trabecular bone, Smith suggested that scans of the distal radius may better reflect loss of mass in the vertebrae (29).

In a 1975 study, Smith with other associates reported results similar to the results of his earlier study (30). Using SPA measurements of the radius in a larger group of fractured (108 women with vertebral body decreased at least one-third in height) and nonfractured (161 women) caucasian women age 50 or older, he demonstrated that the nonfractured group had significantly higher bone mineral values. Again there were significant overlaps between bone mineral values for osteoporotic and for normal subjects. A short followup of 278 women for 470 subject-years showed that women with low SPA measurements may have a greater risk of diverse types of fractures. He found that the incidence of vertebral fractures was inversely proportional to the initial bone mineral measurements taken at the radius (30). Smith concluded, however, that factors other than low bone mineral, such as degree of trauma, quality of bone and activity, may be determinants of fracture as well (30).

In a related study of SPA measurements of rates of mineral loss with aging, Smith and colleagues determined that estimates of rates of loss over periods less than 2 years were too low in precision to be useful (31). According to Smith, if an individual loses bone mineral at an average rate of about 1 percent per year, the precision of the technique which would allow the detection of such a rate must approach 1 percent if the loss is to be determined in 1 year. If the precision is greater than this, several years' time will be needed before the loss can be detected (31).

Similar studies involving bone mineral measurements in osteoporosis were conducted at Brookhaven National Laboratory (32). Cohen and associates attempted to diagnose osteoporosis, based on SPA bone mineral measurements of the radius. Cohen found a large inherent variability in the bone mineral measurements of the radius similar to those reported by Smith (29). He also was unable to normalize the bone mineral measurements for the size, age, and sex of the individual (32). According to Cohen, these factors often make SPA bone mineral measurements of the radius unsatisfactory for evaluation of the extent of osteoporosis in an individual. However, he does believe that bone mineral measurements on the radius can be used to distinguish an osteoporotic population from an age- and sex-matched normal population.

In a continuation of the work by Cohen (32), Aloia and coworkers determined whether changes in bone mineral measured by SPA in the midradius (8-cm site), following therapy for osteoporosis, reflected changes in skeletal mass (total-body calcium) as measured by total-body neutron activation analysis (TBNAA) (33). Thirty-six osteoporotic patients who underwent several therapeutic regimens were studied on two occasions approximately 9 months apart by SPA and TBNAA. Aloia found no apparent relationship between the changes in bone mineral measured by SPA in the midradius with the changes in total-body calcium. Aloia concluded that changes in bone mineral at the midradius (8-cm site) could not be extrapolated to indicate changes in skeletal mass. However, he noted that it was possible that differential rates of remodeling occurred

with therapy in various skeletal sites and that an increment in BMC of the radius could be accompanied by a decrement in total skeletal mass (33). Although Aloia suggested that a better correlation between SPA measured changes in bone mineral with changes in total-body calcium might have been obtained at a radial site with more trabecular bone (3-cm site), this site was not utilized because of its increased error in measurement (33).

Studies by Khairi and coworkers and Wahner and associates, published in 1976 and 1977 respectively, used SPA and Singh's Trabecular Pattern Index (Singh index) to assess skeletal status and to compare the ability of the two methods to single out osteoporosis-prone subjects (34,35). Both groups reported that neither of the methods clearly separated the subjects with fracture from those without fracture. The study by Khairi prospectively followed 106 women, 70 to 95 years old, for 2 to 3 years after obtaining initial SPA bone mineral measurements and a Singh index (34). Noting that the total numbers of subjects and fractures (n=29) were few, Khairi reported that the incidence of subsequent fractures showed a significant inverse correlation with the initial SPA bone mineral measurements at the distal radial site (34).

The data published by Wahner again confirmed that SPA bone mineral measurements of osteoporotic patients fall within the lower ranges of average bone mineral of the relevant cohorts (35). In his study, and in contrast to the findings of Khairi, Wahner found that the Singh index gave a better separation of osteoporotic patients and age-matched normals than SPA measurements. According to Wahner, the Singh index, which is based entirely on changes in trabecular bone, probably discriminates better because osteoporotic patients have a greater proportion of loss of trabecular bone of the axial skeleton than of cortical bone of the appendicular skeleton (35).

In 1981 Riggs and coworkers at the Mayo Clinic demonstrated differences in trabecular and cortical bone diminution in elderly normal subjects and in patients with spinal osteoporosis (36). In a cross-sectional study, Riggs compared trabecular and cortical bone diminution with aging by measuring bone mineral concurrently at sites in

the axial and appendicular skeleton. Bone mineral of the radius (mid and distal) was measured by SPA while bone mineral of the vertebrae was determined by DPA. According to Riggs, although there was still considerable overlap, spinal bone mineral measurements with DPA were able to discriminate patients with osteoporosis from age- and sex-matched normal subjects better than SPA bone mineral measurements on the radius (36). Riggs suggested that cortical bone and trabecular bone function as separate compartments, which differ in respect to onset and rate of bone loss. He concluded that direct spinal measurements of bone mineral are greatly superior to appendicular measurements for evaluating the severity of spinal osteoporosis (36).

According to the work of Manicourt and associates, however, the amount of bone estimated by SPA measurements at the distal radius (3-cm site) closely correlates with the amount of bone estimated by physical determination of porosity index in the iliac crest trabecular bone (37). Bone biopsy and SPA measurements were performed concomitantly on 40 subjects: 31 normal and 9 patients with one or more compression fractures of the vertebrae. Because the physiochemical data (i.e., porosity index) correlated with the bone mineral values, Manicourt suggested that SPA measurements of a single peripheral bone (radius) are representative of changes in the axial skeleton in normal and osteoporotic subjects. He also indicated that distal scans of the radius better reflected the axial skeleton mass than proximal scans (37).

In 1983 Jensen and colleagues reported finding a relationship between SPA bone mineral measurements in the distal part of the forearm of 70-year-old women and the frequency of postmenopausal fractures (38). In the 258 women studied they identified 131 osteoporotic fractures, i.e., vertebral, hip, proximal humerus, and distal forearm in 77 of the women. The main observation of the author was that the frequency of osteoporotic fractures was more than three times higher in the 40 percent of women with

the lowest bone mineral values than in the 20 percent of women with the highest values. Jensen concluded that there is an increased frequency of osteoporotic fractures associated with decreased SPA bone mineral measurements in the forearm (38).

Recently, Gupta and coworkers reported using SPA measurements to establish the presence of and/or determine the severity of osteoporosis (39). In 13 of 17 patients with a history of vertebral compression fractures they found reduced bone mineral values at the radial shaft. However, 4 patients (24 percent) with compression fractures had normal bone mineral values and 24 patients without fractures had reduced bone mineral values at the radial shaft. Gupta concluded that SPA measurements of the raidal shaft may not accurately reflect the state of the axial skeleton. He suggested, despite repositioning error, considering SPA measurements of the distal end of the radius or direct measurements of the axial skeleton by DPA (39).

Similar findings and conclusions regarding the relationship between radius and spinal bone mineral measurements were also reported by Mazess and associates (6). In that study, reported in 1984, SPA bone mineral measurements of the distal third of the radius (site one-third of the forearm length proximal to the styloid process of the ulna) were compared with DPA total-body bone mineral measurements (TBBM) and spinal measurements in normal and osteoporotic subjects. Mazess found in normal males and females, a relatively small error (6-10 percent) in estimating the status of the total skeleton or the spine from SPA bone mineral measurements on the radius (6). However, in osteoporotics there was little relation between measurements at these sites. According to Mazess, in metabolic bone disease such as osteoporosis, a preferential alteration of trabecular bone makes measurements at appendicular sites (radius) inappropriate. He concluded that preferential spinal osteopenia probably explains the poor diagnosis of osteoporosis based on forearm measurements and confirms the need for a direct measurement of trabecular bone at the spine (6).

The regions of the radius examined in most of the previously discussed studies have been composed mainly of cortical bone. Reference to these regions as 10 percent, one-third, and 50 percent sites technically refer to the length along the ulna. According to Schlenker and von Seggen's distribution of BMC and percentage of trabecular bone along the radius, the percentage of trabecular bone at the 10 percent site is less than 25 percent and the percentage of trabecular bone at the one-third and 50 percent sites is less than 10 percent (40). These sites are mainly cortical bone whereas the site of interest, the vertebrae, is predominantly trabecular bone.

Therefore, more recently, groups have reported their experience using SPA to study the radius at a site where the percentage of trabecular bone is similar to that found in the lumbar spine. This region on the radius has been referred to as the "distal or ultradistal site," and is determined by a specific radius-ulna gap. Distal radial bone mineral studies with SPA at a 5mm site (radius-ulna gap) have been performed by various groups, under the direction of Talmage, at the University of North Carolina School of Medicine. In one of those studies, Aubrey and associates determined the reliability of SPA measurements at the 5 mm distal radius site. In a cross-sectional study of more than 700 normal white women they obtained measurements at the 5 mm site relative to age (41). According to Aubrey use of the 5mm distance between the ulna and radius for SPA positioning allows for reproducible measurements at a distal site. Nonetheless, he showed that mispositioning at the 5mm site could result in measurement errors of 1 to 3 percent (41). However, he demonstrated a trabecular bone composition of greater than 50 percent at the 5mm site.

From the large cross-sectional study of 700 normal women ranging in age from 18 to 98 years, Aubrey found that there was minimal bone loss in the radius before the age of 50 (41). This was followed by an accelerated phase of bone loss that persisted for the remainder of life. The bone mineral values at the midradius and distal radius were very similar. To determine if the distal radius measurements were indicative of conditions

existing in the spine, Aubrey compared the SPA distal radius measurements to DPA lumbar bone measurements in 140 normal subjects (41). Based on the small population tested, Aubrey concluded that in "normal" women the bone loss with age at the distal radius 5 mm site correlated closely with generalized bone mineral loss of the axial skeleton.

In a subsequent study, by the same group, Grubb measured radius and lumbar spine bone density in a small population of postmenopausal white female patients with nontraumatic fractures and their age-matched controls (42). An osteopenic group without fractures was also examined. He found that bone density values at all sites (midradius, and distal radius and spine) in the patient populations were statistically reduced from the bone density values in the control population. While the density of the midradius in two patient groups (mean age 62 years) showed a 12 percent decrease in density from the control values, the density of both the lumbar vertebrae and the distal radius had decreased 25 percent. From an analysis of his measurements in patients, Grubb found a statistically significant correlation coefficient of 0.51 between bone density of the distal radius (5 mm site) and that of the lumbar spine. He concluded that in patients as well as controls, the density of the distal radius correlates well with that of the lumbar vertebrae (42).

According to Grubb, 95 percent of all the patients with nontraumatic fractures of the spine and hip had a distal radius density value of 325 mg/cm^2 or less (42). Based on this finding, he suggested that patients without fractures but with distal radius density values below this "at risk" value (325 mg/cm^2) be considered for further evaluation. However, almost 30 percent of the women with "at risk" distal radius measurements had normal lumbar bone measurements.

In an accompanying cross-sectional study, Jacobson and coworkers used SPA bone density measurements at the distal radius site of 5 mm to determine the effects of exercise on normal postmenopausal bone loss (43). Bone density also was measured at the

midradius and first metatarsal with SPA and at the spine with DPA. By comparing the bone density of women college athletes with non-athletes and adult athletic women with non-athletic women, Jacobson found that women who exercise regularly and intensely have elevated bone mass both in compact and trabecular areas. According to Jacobson, bone measurement values in the radius and lumbar spine in the oldest athletic group (55-75 years of age) were in the same range as for younger athletic women. Jacobson concluded that while the data suggest that a regular and sustained exercise program is beneficial in building and maintaining bone mass in women, longitudinal studies have to be carried out before the beneficial effects of exercise on adult bone mass could be thoroughly established (43).

In a similar cross-sectional study using SPA to examine appendicular trabecular bone in normal women, Nilas and colleagues reported that on a group basis, the bone loss at the distal forearm scan site corresponds to the spinal bone loss (4). However, because the relationships between forearm and spinal bone masses are modest, Nilas concluded that in individuals, spinal bone mineral cannot be predicted from bone measurements taken at the forearm. To measure appendicular trabecular bone, Nilas located the 8 mm site (radius-ulna gap) and scanned distally with 4 additional scans 2 mm apart. By comparing bone measurements in this site in 19 postmenopausal and 53 premenopausal women with bone measurements scanned proximal of the 8 mm site (cortical bone), Nilas found that postmenopausal trabecular bone loss was approximately seven times greater than cortical loss within the first 5 to 6 postmenopausal years (4).

According to Nilas, the normal calibration procedure usually recommended by the manufacturers of a single measurement of the standard before each patient is examined is insufficient and results in a precision of 2 to 3 percent (4). To eliminate machine drift and achieve a long-term reproducibility of 1 to 1.5 percent, Nilas also calibrated the system once a week by measuring an aluminum standard nine times for 54 scans.

In their review of the Nilas study and other studies using SPA to measure bone mineral at distal and ultradistal sites on the radius (and ulna), Wahner and colleagues suggested that measurements made at these sites be interpreted with caution until further data are available (5). According to Wahner, although investigators determine and use the correlation coefficient between bone density of the ultradistal radius and that of the lumbar spine to show a relationship between the two, it is not the appropriate parameter for predicting lumbar spine density from ultradistal radius density in an individual. He believes that the appropriate parameter is the 95 percent confidence interval (5). Wahner showed that studies in which the correlation coefficient was statistically significant (0.56) between bone density of the ultradistal radius and that of the lumbar spine could also have 95 percent confidence intervals of $\pm$ 22 percent. Wahner found similar 95 percent confidence intervals are obtained when predicting lumbar spine density from age alone (5).

Mazess has also reviewed the studies using SPA for measurements of the distal radius (44). He is in agreement with Wahner that correlation coefficients between bone density of the ultradistal radius and that of the lumbar spine are not the appropriate parameters for predicting lumbar spine density from ultradistal radius density in an individual. According to Mazess it would be impossible to accurately predict spinal density from the distal radius when the correlation was only 0.52 (44). He also argues that the 5 mm site, measured by some investigators, while containing more than 35 percent trabecular bone is not 50 percent as indicated. According to Mazess, studies thus far have not shown that the distal radius site is a better discriminator of osteoporosis than the radius shaft or is equal to the spine (44).

Recently, at the Garvan Institute of Medical Research in Australia, Pocock and coworkers examined the correlation between distal (8 mm) forearm BMC determined by SPA, and lumbar vertebral and femoral neck BMD determined by DPA (45). Significant correlations (p less than 0.001) were found between the measurements on the forearm

and at the two axial sites in their study of 80 women, 50 postmenopausal, aged 20 to 76 years. However, despite the significant correlation between BMD in the spine and hip and BMC of the forearm, there was a large scatter of individual values about the regression line (large standard error of the regression). According to the authors the standard error of the regression (13 percent spine and 12 percent hip) was too large to allow reliable prediction of either site from the other in a particular individual (45).

Pocock took different forearm BMC's as detection points and determined the sensitivity and specificity of SPA for lumbar spine mineral density below 0.97g/cm^2 (a value associated with increased fracture risk) (45). For prediction of lumbar spine osteopenia with a sensitivity of 88 percent, Pocock determined that the false positive rate was 91 percent. In order to achieve a specificity of 82 percent, Pocock found the false negative rate was 65 percent. Similar predictions were obtained at the femoral neck. Pocock concluded that despite the relatively small study population, the data show that forearm densitometry (8 mm site) cannot be used to detect (screen) reduced BMD in the lumbar vertebrae or femoral neck in postmenopausal females (45).

In a longitudinal study of 1,098 randomly selected women ranging in age from 43 to 80 years, Wasnich and associates determined the risk of fracture associated with varying photon absorptiometry BMC measurements at four skeletal sites (46). BMC of the os calcis, distal radius, and proximal radius was measured by SPA in all 1,098 women. These women have now been followed for 4.5 years. Of these women, 456 have had (subsequent to fracture occurrence) both lumbar spine scans (DPA) and x-rays. Among the 1,098 women followed for 4.5 years there were a total of 26 incident fractures. These included eight rib fractures, six fractures at the wrist and only one at the hip (46).

Wasnich compared the nonspine fracture incidence rates by quintile of bone mineral content at the proximal radius, distal radius, os calcis, and lumbar spine (46). Using estimated odds ratios for varying levels of BMC, he investigated the dose-response

relationship of BMC to the risk of fracture. Wasnich determined that the risk of fracture was significantly increased with diminishing quintiles of BMC at most skeletal sites. Moreover, when subjects in the lowest BMC quintile were compared to those in the highest quintile, the greatest risk difference was found for the os calcis.

Because subjects in the lowest quintile of os calcis BMC had a nonspine fracture risk 10 times greater than subjects in the highest BMC quintile, Wasnich concluded that the os calcis BMC measurement was the best predictor of nonspine fracture risk (46). This would include hip fractures, although only one fracture at that site was included in the study. He also suggested, based on prevalence data, that the os calcis BMC measurement was the best overall indicator of spine fracture risk. The most significant relationship of BMC to spine fracture prevalence was observed for the os calcis ($p=0.026$) and the lumbar spine ($p=0.041$). Although the study did not relate BMC at the os calcis to subsequent spinal fracture incidence, Wasnich concluded that measurement of os calcis BMC may be useful for routine risk evaluation of perimenopausal women (46).

In a related study, Wasnich included prospective spinal fracture incidence data in order to evaluate the predictive power of photon absorptiometric bone mineral measurements at various sites for fracture risk at "all" skeletal sites combined (47). He hoped to determine which single skeletal measurement was the best predictor of fracture risk, irrespective of fracture site. Also, the small number of spinal incident fractures recorded may have necessitated combining the spine and appendicular incident fractures.

The 294 women of this study, ranging in age from about 44 to 79 years, were a random subsample of the population described in the previous report (46). A total of 17 incident fractures were observed which included 8 at the spine and 1 at the hip. Wasnich observed the most significant relationships of BMC to fracture risk for the os calcis ($p=0.009$) and the spine ($p=0.011$). When subjects in the lowest BMC quintile were

compared with those in the highest, the greatest risk difference was found for the os calcis. Subjects in the lowest quintile of os calcis BMC had a combined (global) fracture risk six times greater than subjects in the highest BMC quintile.

Wasnich concluded, however, that because of the small number of incident fractures, these results must be viewed as preliminary. He suggested that measurements at the os calcis and lumbar spine may prove to be useful for assessment of global (total) fracture risk (47).

In a followup to the previous work at North Carolina, Talmage and coworkers used SPA and DPA to study age-related bone loss at several skeletal sites (48). Bone mineral density was measured at the midradius, distal radius and lumbar spine in 1,105 asymptomatic non-athletic and 124 athletic Caucasian women aged 18-98 years.

In the non-athletes, Talmage observed that the BMD of the two radial sites and the lumbar spine correlated positively (48). He also found that an age-related increase in rate of loss of BMD occurred at each of the three sites. The approximate age at which the increase in the rate of BMD loss occurred corresponded roughly to the time of menopause. In order to explain the increase in rate of loss of BMD at the spine, not seen in other reports (36), Talmage indicated that this may be due to differences in sample size and the age distribution of the populations studied (48).

In the smaller population of athletes, defined as those women who exercised regularly three times per week for 9 months of the year for at least 5 years, no increase in the rate of bone density loss could be demonstrated at the two radial sites (48). The number of lumbar spine measurements (DPA) in this group was too small for analysis. According to Talmage, while the absence of a significant change in rate of bone loss in athletes could have been due to the relatively small number of subjects, it also suggested that regular sustained exercise programs may delay or minimize the increased rate of loss of BMD which occurs in non-athletic women in the perimenopausal period (48).

In contrast to the findings of Talmage (48), Riggs again reported finding striking differences in the patterns of appendicular and axial bone loss, over life, in women (49). Based on a longitudinal study of only 139 normal women aged 20-88 years, he concluded that vertebral bone loss began well before menopause and continued into old age, with only a trend toward midlife acceleration. According to Riggs, substantial amounts of bone lost from the axial skeleton prior to menopause suggest prophylactic intervention well before the menopause (49).

Recently, Ott and coworkers found that in women with osteoporosis there were no correlations between SPA, DPA, and CT measurements of 1-year changes in bone mass (50). In addition to the possibility of different rates of bone changes at different sites of the skeleton, Ott suggested that the lack of correlation between the measurements may be related to the precision of the techniques and magnitude of the changes in bone in osteoporosis. She concluded that the techniques used were not sufficiently precise to measure the small amount of change in bone after only 1 year (50). Riggs and Melton believe that measurements every 6 months over 2 to 3 years may be required to estimate individual rates of bone loss (21).

According to Ruff and Hayes, changes in bone geometry and in material properties, such as ultimate compressive and tensile strength and energy absorbed prior to failure, may be the most critical features of the skeletal aging process (51). Failure to measure these characteristics may account for the relatively low efficiency of photon absorptiometry in identifying individuals who are at high risk for fracture. Moreover, they believe that standardizing BMC by bone width can produce misleading results in locational, sex, and age comparisons. In order to compare BMC in different individuals, some kind of standardization of skeletal size (bone volume) must be carried out (51). The most common size-standardization procedure has been to divide BMC by total bone width across the path of the scan (1). However, based on a 1984 study, Ruff and Hayes do not

believe that bone width is a good index of true bone volume and suggest that variations reported in bone mineral mass are almost entirely due to variation in bone volume, not variation in bone density or mineralization (51).

DISCUSSION

The measurement of bone mass is an important tool in the study of metabolic bone diseases, particularly osteoporosis. Current interest is centered on the recent advances in the SPA technique. This interest is a result of the recent applicability of the SPA technique to measure appendicular bone sites (distal radius, os calcis) with quantities of trabecular bone similar to that of the spine and hip. While SPA is capable of measuring bone mineral and has advanced our knowledge of bone disease in general, its role in the management of the individual patient is uncertain.

It would be advantageous to be able to prospectively identify those women who are at risk of developing osteoporotic fractures, in order to direct treatment to those at greatest risk. As a screening test for osteoporosis in perimenopausal women, this application of SPA bone mineral measurements is suggested to have potential utility. Once established as a screening tool it could be used in the strategy for treating afflicted individuals or preventing osteoporosis. Although the technology to noninvasively measure bone mineral with SPA is currently available, the ability of such measurements to identify those individuals who will subsequently fracture has not yet been shown. In a prospective study of 1,098 women with diverse types of nonvertebral fractures, Wasnich and coworkers found that subjects in the lowest quintile of bone density, as measured by SPA, had a tenfold greater risk of some type of fracture than women in the highest quintile (46). Measurements of the bone density of the os calcis appeared to be a stronger predictor of fractures than measurements at other sites. According to other investigators, this study included too few fractures of the hip (one) or wrist (six) to assess

the value of SPA for predicting these fractures (52). In a subsequent study by Wasnich, which included prospective vertebral fracture incidence data, the author recommended that the results of that study be viewed as preliminary because of the small number of incident fractures included in the study (47).

Presently, there has been no prospective study demonstrating that the noninvasive measurement of bone mass by SPA can identify patients who will suffer fractures. In their 1984 review of the various noninvasive methods for bone mineral measurements, Wahner and colleagues concluded that there was no optimal technique available for mass screening for early osteoporosis (1). The American College of Physicians' Health and Public Policy Committee recently reviewed various radiologic methods for measuring BMD, including SPA, but made no recommendation about the use of these tests in routine screening for osteoporosis (2). In order to predict individuals' fracture risk, it would be necessary to study large population cohorts of women from various age groups and relate their specific bone measurements to prospective fracture incidence data collected over a sufficient period of time. From fracture incidence data, the risk ratio would provide an estimate of risk. This type of study would enable investigators to determine whether it would be possible to predict the risk of fracture from the initial bone density measurements. A patient's bone mass measured before or at menopause may indicate whether she has low or high bone mass for her age. It will not necessarily indicate whether she will fall into the high-risk group 10 to 15 years later, when fractures begin. The contribution of bone mass at maturity versus subsequent rates of loss is still largely unknown. Moreover, there exists a controversy regarding the selection of a screening site. While many investigators consider BMD measurements of the actual fracture site (spine and hip) paramount, others argue that fracture risk prediction and screening can be accomplished by appendicular (trabecular) BMD measurements.

According to some reports it would be a useful screening tool (42,46). However, according to other reports it would be of little value because it could not reliably predict the risk of fracture in the spine or hip (21,45).

Initially, investigators used SPA bone mineral measurements in attempts to find a specific level of bone density that clearly distinguished patients with vertebral osteoporosis. Those studies, including the work of Smith and associates (30), Cohen and associates (32), Khairi and coworkers (34), and Wahner and associates (35), have been largely unsuccessful. According to Smith, factors other than low bone mineral, such as degree of trauma, quality of bone, and activity, may be determinants of fracture as well. An individual subject with low bone mineral has only one of the factors which increases the risk of fracture (30). Although Cohen found SPA bone mineral measurements of the radius unsatisfactory for evaluation of the extent of osteoporosis in an individual, he believes that bone mineral measurements on the radius can be used to distinguish an osteoporotic population from an age- and sex-matched normal population (32).

Other published reports also suggest that forearm SPA would not reliably assess the state of the spine or hip. Mazess and colleagues found in normal males and females, a relatively small error (about 10 percent) in estimating the status of the spine from SPA bone mineral measurements on the radius (6). However, in osteoporotics there was little relation between measurements at these sites. According to Mazess, 30 to 40 percent of patients at risk will be missed by SPA measurements, even if those measurements are taken on the distal radius or the os calcis (53). Mazess concluded that preferential spinal osteopenia probably explains the poor diagnosis of osteoporosis based on forearm measurements and confirms the need for a direct measurement of trabecular bone at the spine (6).

Recently, studies of SPA have attempted to determine the clinical usefulness of SPA measurements at appendicular sites (distal and ultradistal radius) containing amounts of trabecular bone similar to that found in the lumbar spine. Jacobson (43) and Talmage (48) at the University of North Carolina School of Medicine used SPA measurements at the distal radius (5 mm site) to show differences in bone mass and bone loss in groups of atheltic and non-athletic women. In an accompanying study, Grubb found a statistically significant correlation between bone density of the distal radius and that of the lumbar spine. He concluded that in patients as well as controls, the density of the distal radius correlates well with that of the lumbar vertebrae (42).

However, studies by Nilas (4), Wahner (5), Mazess (44), and Pocock (45), indicate that a significant correlation between measurements at two sites (distal radius and lumbar spine) does not necessarily mean that one measurement may accurately predict the other. Although Nilas found that bone loss at the distal forearm scan site corresponded to spinal bone loss, he concluded that in individuals, spinal bone mineral could not be predicted from bone measurements taken at the forearm (4). Wahner showed that in the Nilas study, in which the correlation coefficient between bone density of the ultradistal radius and that of the lumbar spine was statistically significant, scatter of the data could result in an error in measurement prediction of $\pm$ 22 percent (5). According to Wahner the appropriate parameter for predicting lumbar spine density from ultradistal radius density in an individual is the 95 percent confidence interval.

Pocock and coworkers also found a significant correlation between BMD in the spine and hip and BMC of the forearm (8 mm site). However, he also reported that there was a large scatter of individual values about the regression line (large standard error of the regression). According to Pocock, significantly correlated measurements with a large standard error of the regression (scatter) will preclude a reliable prediction of one site from the other in a particular individual (45).

Moreover, as a screening technique for reduced BMD in the lumbar spine, Pocock showed that a sensitivity of 90 percent with SPA could only be achieved by accepting a specificity of 9 percent (45). This meant a false positive rate of about 90 percent. Similarly, for prediction of femoral neck osteopenia at a SPA sensitivity of 92 percent, Pocock found that the false positive rate was 87 percent.

Another clinical application proposed for the SPA technique has been the use of SPA measurements to monitor the rates of bone loss and the effectiveness of treatment. This could apply to the treatment of individuals with established osteoporosis and also to those receiving preventive regimens. Because rates of bone loss are relatively small compared with the reproducibility of the measurement, current methods for measuring bone mass, including SPA, may not be sufficiently precise for clinical decisions in an individual (52,54). SPA is reported to have a precision of 1 to 5 percent and the average rate of appendicular bone loss in women is 1 percent per year in the decade after, and less before natural menopause (9,52). According to Cummings and Black, measurement of women's rate of bone loss based on two measurements of bone mass over a period of time leaves considerable uncertainty about her rate of loss. Even a bone loss of 3 percent measured by a technique with a 2 percent reproducibility (SPA) leaves considerable uncertainty about the actual rate of loss (the 90 percent confidence interval for that change in bone mass varies from a 1.7 percent gain to a 7.7 percent loss) (52). Unless multiple measurements are made, a woman must lose a substantial amount of bone during the time between measurements before a physician can conclude that she is losing bone more rapidly than normal (52). However, even these additional measurements have uncertain value for predicting future rates of bone loss or assessing risk for fractures and would substantially increase the expense. According to Ott, until such time as more sophisticated methods of improving the reproducibility are developed, techniques for measuring bone mineral, such as SPA, will be valuable in studying large groups of patients but will not be helpful in individuals (54).

With adequate precision, the high accuracy of SPA, together with its low radiation dose (2-5 mrad), would suggest that it would be particularly suitable for determining rates of bone loss by sequential measurements. However, for single measurements, there would be uncertainty as to whether the results would reliably reflect bone loss in the spine and hip.

Advice and comments concerning the safety and clinical effectiveness of SPA have been sought from groups and organizations within and outside of the Federal Government. An announcement of this assessment appeared in the Federal Register notice of October 26, 1984 (55). On June 20, 1985, in testimony before the Subcommittee on Aging of the Committee on Labor and Human Resources, United States Senate, the National Institutes of Health (NIH) through the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) stated that it was a research imperative to develop methods for measuring bone density (56). In addition to diagnosis, these methods should enable early identification of bones most vulnerable to fracture and provide a measure by which to evaluate the effectiveness of new therapies. According to NIADDK, while several noninvasive methods for measuring bone density have been developed, at present no existing techniques can adequately discriminate early in the disease process between normal and osteoporotic individuals (56). The NIADDK recommended long-term clinical trials of various specific patient populations in numbers large enough to provide valid and reliable estimates of risk, and to determine the optimal regimens to prevent bone loss and fracture.

At that same hearing on osteoporosis, the National Institute on Aging (NIA) stated that there is a need for better ways of identifying persons at high risk of fracture, since those individuals could be expected to benefit most from treatment (20). Because it is still unclear which persons would benefit from which treatments and at what dosages and schedules, additional research and clinical trials are needed to develop the current state of knowledge regarding prevention and treatment of osteoporosis for specific individuals

or groups. The American College of Obstetricians and Gynecologists (ACOG), in their statement before the Subcommittee on Aging, indicated that presently, there are no tests to identify which women are at risk for developing osteoporosis (19). The College recommended, however, that the physician determine bone loss by absorptiometry in their diagnosis of osteoporosis.

Prior to the June 20, 1985, Senate Hearing on Osteoporosis, the National Institutes of Health (NIH) Consensus Development Conference on Osteoporosis was held on April 2-4, 1984 (18). At that conference, data were presented which showed that none of the noninvasive techniques for measuring bone mass were able to discriminate significantly between normal and osteoporotic individuals. None of the techniques for currently quantitating bone mass can definitely predict the individual at significant risk for osteoporosis prior to the occurrence of fracture. The Consensus Panel concluded that osteoporosis was a major public health problem requiring additional research on the biology of human bone, defining individuals at risk, and developing safe, effective, low-cost strategies for fracture prevention (18). The panel recommended studies to develop accurate, safe, inexpensive methods for determining the level of risk for osteoporosis in an individual, to establish early diagnosis, and to assess the clinical causes of the disease (18).

According to the Food and Drug Administration (FDA), SPA devices are pre-amendment products marketed prior to enactment of the Medical Device Amendments of May 28, 1976, to the Food, Drug, and Cosmetic Act. SPA devices are being marketed under Section 510(k) of the Medical Device Amendments to the Food, Drug, and Cosmetic Act. These devices have been proposed for classification as Class II devices.

Through its Clinical Efficacy Assessment Project, the American College of Physicians published a policy statement on radiologic methods to evaluate bone mineral content in June 1984 (2). The College concluded that all methods of BMC measurement result in significant overlap between diseased and normal populations. They stated that

the ultimate benefit of early diagnosis of metabolic bone disease will depend on the clear establishment of safe and effective treatments. The College believes that measurements of BMC have greater utility in following the course of a disease process or assessing the effect of therapy than in establishing a diagnosis. According to the College, none of the available techniques, including SPA, accurately predict tendency to fracture (2).

The Orthopedic Research Society strongly supports continued research in the development of noninvasive techniques for understanding metabolic bone disease. The Society suggested that the research examine the precision, accuracy, sensitivity, cost, availability, and relevance to underlying metabolic bone disease of each of the techniques currently under study. The Society also suggested holding a workshop directed at the understanding of the surveillance of bone disease.

It is the opinion of the Society of Nuclear Medicine that bone mineral density studies should become part of the work-up of patients with osteoporosis and that DPA is the technique of choice at this time. According to the Society, other methods performed on appendicular bone, such as SPA, are of little value in osteoporosis. However, they may have some application in renal bone disease.

A response from the American College of Nuclear Physicians stated that osteoporosis can be detected in its earliest stages by DPA measurements of the vertebral spine. According to the College, in order to postpone or prevent the problems of insidious progressive osteoporosis, early detection and screening by bone mineral analysis of the lumbar spine by DPA is critical. The College finds DPA of the spine far superior to SPA of the radius in detecting most cases of early osteoporosis. They suggest, however, that in older patients with significant degenerative spine disease, SPA measurements may be helpful in the management of an individual patient.

SUMMARY

SPA is a noninvasive radiologic technique used to assess BMC in the appendicular skeleton. A photon beam from a sealed, single, low-energy radioisotope source is directed at a bone of the patient's limb, usually the radius. The difference in photon absorption between bone and soft tissue allows for the calculation of the total bone mineral found in the scan path. With current equipment incorporating a rectilinear scanner and averaging multiple scans, the technique can achieve a precision of 1 to 2 percent with a radiation dose of 2 to 5 mrad.

The measurement of bone mass is an important tool in the study of metabolic bone diseases, particularly osteoporosis. While SPA is capable of measuring BMD and has advanced our knowledge of bone disease in general, its impact on the management of the individual patient is equivocal. Although the technology to measure bone mass noninvasively with SPA is currently available, the ability of such measurements at the os calcis and distal radius to predict individuals at risk of subsequently developing fractures of the spine and hip (screening) has not yet been shown.

Early studies with SPA that attempted to find a specific level of bone density that distinguished patients with vertebral osteoporosis from those without have been largely unsuccessful. Recently, studies with SPA measurements at the distal and ultra-distal radius have reported statistically significant correlations between bone density of the distal radius and that of the lumbar spine. However, a large scatter in the data precludes a reliable prediction of bone mineral from one site to another in a particular individual.

Other clinical applications proposed for the SPA technique have been the use of SPA measurements to monitor rates of bone loss and the effectiveness of treatment. A high degree of precision in the bone mass measurement is necessary for repeated

measurements of small degrees of change and such precision is difficult to attain. Presently, the suitability of the SPA technique for monitoring changes in bone loss is questionable.

Investigators have not distinguished between the use of SPA in clinical research and its role in day-to-day practice. SPA needs to undergo further clinical investigation before it can be recommended for general clinical use.

According to the FDA, SPA devices are pre-amendment products that were being marketed prior to enactment of the Medical Device Amendments of May 28, 1976, to the Food, Drug, and Cosmetic Act. SPA devices are allowed to be marketed pursuant to Section 510(k) of the Medical Device Amendments. Bone densitometers (SPA) have been proposed for classification as Class II devices.

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REFERENCES

1. Wahner HW, Dunn B, Riggs L. Assessment of bone mineral: Part 2. J Nucl Med 1984;25(11):1241-1253.

2. Health and Public Policy Committee, American College of Physicians. Radiologic methods to evaluate bone mineral content. Ann Intern Med 1984;100(6):908-911.

3. ECRI Technology Assessment. Noninvasive bone mineral assessment. J Health Care Technol 1986;2(3):183-200.

4. Nilas L, Borg J, Gotfredsen A, Christiansen C. Comparison of single- and dual-photon absorptiometry in postmenopausal bone mineral loss. J Nucl Med 1985;26:1257-1262.

5. Wahner HW, Eastell R, Riggs BL. Bone Mineral Density of the Radius: Where Do We Stand? J Nucl Med 1985;26:1339-1341.

6 Mazess RB, Peppler WW, Chesney RW, et al. Does bone measurement on the radius indicate skeletal status? Concise Communication. J Nucl Med 1984; 25(3):81-288.

7. Mazess RB. Advances in single- and dual-photon absorptiometry. In: Christiansen C, et al., (eds). Osteoporosis: Proceedings of the Copenhagen International Symposium on Osteoporosis June 3-8, 1984, pp 57-63.

8. Cameron JR, Sorenson J. Measurement of Bone Mineral in-vivo: An improved method. Science 1963;142:230-232.

9. Johnston CC, Jr. Noninvasive methods for quantitating appendicular bone mass. In Avioli LV, (ed). The osteoporotic syndrome: detection, prevention and treatment. Grune and Stratton, NY 1983;73-83.

10. Wahner HW, Dunn WL, Thorsen HC, et al. Bone mineral measurements: review of various techniques. In: Wahner HW (ed) Nuclear Medicine: Quantitative Procedures. Boston, Little Brown and Company, 1983, pp 107-32.

11. National Center for Health Services Research and Health Care Technology Assessment. Public Health Service Assessment, Dual Photon Absorptiometry (In Press).

12. Wahner HW, Dunn WL, and Riggs BL. Assessment of Bone Mineral. Part 1. J Nuc Med 1984;25:1134-1141.

13. Griffiths HJ, Zimmerman RE. The clinical application of bone mineral analysis. Sekeltal Radiology 1978;3:1-9.

14. Stewart WK, Fleming LW, Hutchinson F. Bone mineral content measured by direct photon absorptiometry in a normal population and in patients on maintenance haemodialysis. Scottish Medical Journal 1973, 114-118.

15. Muirhead N, Kerr DNS, Ward MK and Aird EGA. Osteoporosis in renal diseases and dialysis. In: Dixon RGG, Russell and Stamp TCB (eds). Osteoporosis, a multi-disciplinary problem. Royal Society of Medicine International Congress and Symposium Series No. 55, published jointly by Academic Press Inc. (London) LTD, and the Royal Society of Medicine. 1983;173-177.

16. Griffiths HJ, Zimmerman RE, Bailey G. The correlation of radiographic bone surveys with bone mineral values obtained using a photon absorptiometric technique in a group of 315 patients with chronic renal failure - A preliminary report. In: Mazess RB, (ed). Proceeding of the International Conference on Bone Mineral Measurement. Chicago, Illinois, October 12-13, 1973. DHEW Publication No. (NIH) 75-683.

17. Atkinson PJ, West RR, Parsons FM, Reed GW. Loss of skeletal calcium by patients on maintenance dialysis. British Medical Journal 1970;3:490-92.

18. Anonymous. Osteoporosis. Concensus Conference. JAMA 1984;252(6):799-802.

19. Anonymous. Statement of the American College of Obstetricians and Gynecologists at the Osteoporosis Hearing of the Subcommittee on Aging, Senate Committee on Labor and Human Resources June 20, 1985.

20. Anonymous Statement of the National Institutes of Aging at the Osteoporosis Hearing of the Subcommittee on Aging, Senate Committee on Labor and Human Resources June 20, 1985.

21. Riggs LB, Melton LJ. Involutional osteoporosis. N Engl J Med 1986;314: 1676-1686.

22. Melton LJ, Riggs BL. Epidemiology of age-related fractures. In Avioli LV, (ed). the osteoporotic syndrome: detection, prevention, and treatment. Grune and Stratton, NY 1983;45-72.

23. Judy, PF. Physical aspects of ^{125}I bone absorptiometry. Proceedings: International Conference on Bone Mineral Measurement. Chicago, Illinois, October 12-13, 1973. DHEW Publication No. (NIH) 75-683.

24. Sorenson JA, Cameron JR. A reliable in vivo measurement of bone-mineral content. J Bone and Joint Surg 1967;49-A(3):481-497.

25. Christiansen C, Rodbro P, & Jensen H. Bone mineral content in the forearm measured by photon absorptiometry. Scand J Clin Lab, Invest 1975;35:323-330.

26. Cameron JR, Mazess RB, and Sorenson MS. Precision and accuracy of bone mineral determination by direct photon absorptiometry. Investigative Radiology 1986;3:141-150.

27. Rustgi SN, Siegel JA, Braunstein M, et al. Accuracy of bone mineral data. AJR 1980;135:275-277.

28. Chestnut CH. Noninvasive techniques in the diagnosis of osteoporosis. Presented at the National Institutes of Health Consensus Development Conference on Osteoporosis, April 2-4, 1984.

29. Smith DM, Johnston CC, Jr, and Yu-Pao-Lo. In vivo measurement of bone mass. JAMA 1972;219(3):325-329.

30. Smith DM, Khairi MRA, and Johnston CC Jr. The loss of bone mineral with aging and its relationship to risk of fracture. J Clin Invest 1975;56:311-318.

31. Smith DM, Norton JA Jr., Khairi R, and Johnston CC Jr. The measurement of rates of mineral loss with aging. J Lab Clin Med 1976;87(5):882-892.

32. Cohn SH, Ellis KJ, Wallach, et al. Absolute and relative deficit in total-skeletal calcium and radial bone mineral in osteoporosis. J Nucl Med 1973;15(6):428-434.

33. Aloia JF, Ellis K, Zanzi I, and Cohn SH. Photon absorptiometry and skeletal mass in the treatment of osteoporosis. J Nucl Med 1974;16(3):196-199.

34. Khairi RA, Cronin JH, Robb JA, et al. Femoral trabecular-pattern index and bone mineral content measurement by photon absorption in senile osteoporosis. J Bone Joint Surg 1976;58A(2):221-226.

35. Wahner HW, Riggs BL, Beabout JW. Diagnosis of osteoporosis: Usefulness of photon absorptiometry at the radius. J Nucl Med 1977;18:432-437.

36. Riggs BL, Wahner HW, Dunn WL, et al. Differential changes in bone mineral density of the appendicular and axial skeleton with aging. J Clin Invest.1981;67:328-335.

37. Manicourt DH, Orloff S, Brauman J, and Schoutens A. Bone mineral content of the radius: Good correlations with physiochemical determination in iliac crest trabecular bone of normal and osteoporotic subjects. Metabolism 1981;30 (1):57-62.

38. Jensen GF, Christiansen C, Boesen J, et al. Relationship between bone mineral content and frequency of postmenopausal fractures. Acta Med Scand 1983;213:61-63.

39. Gupta S, Luna E, Belsky J, et al. Photon absorptiometry for non-invasive measurement of bone mineral content. Clin Nucl Med 1984;9:435-439.

40. Schlenker RA, von Seggen WN. The distribution of cortical and trabecular bone mass along the lengths of the radius and ulna and the implications for in vivo bone measurements. Calcif Tissue Res 1976;20:41-52.

41. Awbrey BJ, Jacobson PC, Grubb SA, et al. Bone density in women: A modified procedure for measurement of distal radial density. J Orthop Res 1984; 2(4):314-321.

42. Grubb SA, Jacobson PC, Awbrey BJ, et al. Bone density in osteopenic women: A modified distal radius density measurement procedure to develop an "At risk"-value in screening women. J Orthop Res 1984;2(4):322-327.

43. Jacobson PC, Beaver W, Grubb SA. et al. Bone density in women: College athletes and older athletic women. J Orthop 1984;2(4):328-331.

44. Mazess RB. Bone density reports questioned. Letters to the Editor. J Orthop Res (In Press).

45. Pocock NA, Eisman JA, Yeates MG, et al. Limitations of forearm bone densitometry as an index of vertebral or femoral neck osteopenia. J Bone Min Res 1986:4(1):369-375.

46. Wasnich RD, Ross PD, Heilbrun LK, and Vogel JM. Prediction of postmenopausal fracture risk with use of bone mineral measurements. Am J Obstet Gynecol 1985;153:745-751.

47. Wasnich RD, Ross PD, Heilbrun LK, and Vogel JM. Selection of the optimal skeletal site for fracture risk prediction. In Press: Clinical Orthopaedics and Related Research.

48. Talmage RV, Stinnett SS, Landwehr JT, et al. Age-related loss of bone mineral density in nonathletic and athletic women. Bone and Mineral 1986; 1:115-125.

49. Riggs LB, Wahner HW, Melton III LJ, et al. Bone loss in the appendicular and axial skeletons of women. J Clin Invest 1986;77:1487-1491.

50. Ott SM, Kiloyne RF, Chestnut III CH. Longitudinal changes in bone mass after one year as measured by different techniques in patients with osteoporosis. Calcif Tissue Int 1986;39:133-138.

51. Ruff CB, Hayes WC. Bone mineral content in the lower limb. J Bone Jt Surg 1984;66-A(7):1024-1031.

52. Cummings SR, Black D. Should perimenopausal women be screened for osteoporosis? Ann Intern Med 1986;104:817-823.

53. Mazess RB. Techniques for measuring bone loss: A comparative review. In Update on Postmenopausal Osteoporosis: Selected Proceedings from the Fourth International Congress on the Menopause, Lake Buena Vista, Florida, October 28 - November 2, 1984. Biomedical Information Corporation 1984;38-41.

54. Ott S. Should women get screening bone mass measurements? Ann Intern Med 1986;104(6):874-876.

55. Federal Register 1984;49(209):43115.

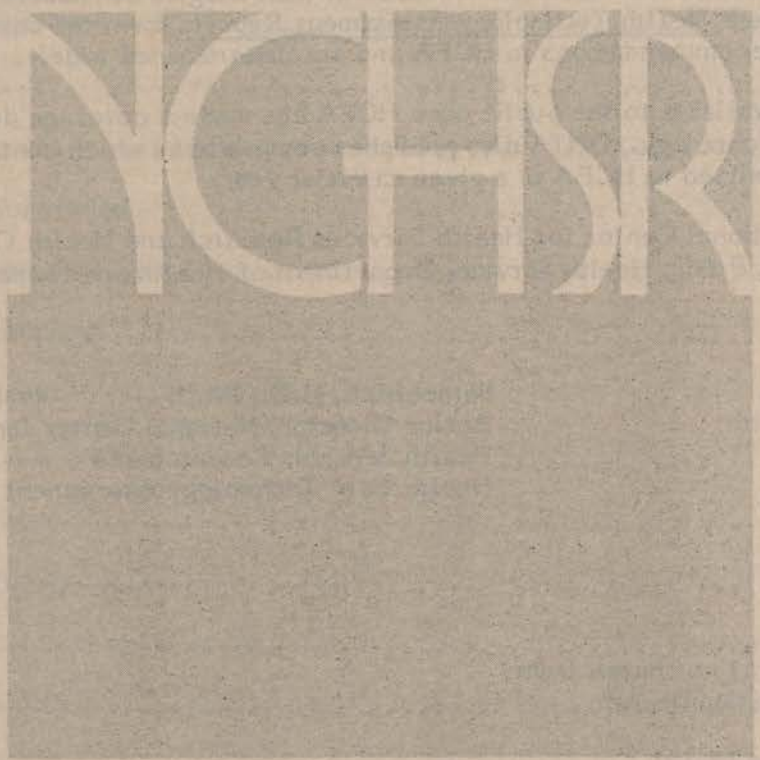
56. Anonymous. Statement of the National Institutes of Arthritis, Diabetes, Digestive and Kidney Diseases at the Osteoporosis Hearing of the Subcommittee on Aging, Senate Committee on Labor and Human Resources. June 20, 1985.

APPENDIX II - Public Health Service Assessment of Dual Photon Absorptiometry for Measuring Bone Mineral Density - 1986

Health Technology Assessment Reports, 1986

Dual Photon Absorptiometry for Measuring Bone Mineral Density

Number 6



NATIONAL CENTER FOR HEALTH SERVICES RESEARCH AND HEALTH CARE TECHNOLOGY ASSESSMENT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

FOREWORD

The Office of Health Technology Assessment (OHTA) evaluates the safety and effectiveness of new or unestablished medical technologies that are being considered for coverage under Medicare. These assessments are performed at the request of the Health Care Financing Administration (HCFA). They are the basis for recommendations to HCFA regarding coverage policy decisions under Medicare.

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OHTA's assessment process includes a comprehensive review of the medical literature and emphasizes broad and open participation from within and outside the Federal Government. A range of expert advice is obtained by widely publicizing the plans for conducting the assessment through publication of an announcement in the Federal Register and solicitation of input from Federal agencies, medical specialty societies, insurers, and manufacturers. The involvement of these experts helps assure inclusion of the experienced and varying viewpoints needed to round out the data derived from individual scientific studies in the medical literature. After OHTA receives information from experts and the scientific literature, the results are analyzed and synthesized into an assessment report. Each report represents a detailed analysis of the safety, clinical effectiveness, and uses of new or unestablished medical technologies considered for Medicare coverage. These Health Technology Assessment Reports form the basis for the Public Health Service recommendations to HCFA and are disseminated widely.

Individual reports are available to the public once HCFA has made a coverage decision regarding the subject technology. OHTA also publishes compilations which contain all assessment reports submitted to HCFA in a given calendar year.

OHTA is part of the National Center for Health Services Research and Health Care Technology Assessment, Public Health Service, Department of Health and Human Services.

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PUBLIC HEALTH SERVICE ASSESSMENT
DUAL PHOTON ABSORPTIOMETRY
FOR MEASURING BONE MINERAL DENSITY
1986

INTRODUCTION

Dual photon absorptiometry (DPA) is a noninvasive radiologic technique used to measure bone mineral density (BMD) in the lumbar spine (vertebrae) and proximal femur (hips). It can also be used to measure total skeletal calcium (1). The technique measures the transmission of a collimated beam of photons after they have been attenuated by bone and soft tissue. As the beam passes through the bone and soft tissue, some photons are absorbed, and a nuclear counting instrument measures the intensity of the beam that emerges. The difference in photon absorption between bone and soft tissue allows for the calculation of the total bone mineral found in the scan path (2). The amount of skeletal mineral present is proportional to change in beam intensity over the bone. The value of bone mineral given by DPA is determined by a calibration with known ash weights of lumbar vertebrae (in grams) L2-L4 or portions of the femoral neck or trochanter per area of bone scanned (in square centimeters). The DPA technique provides no information about the volume of bone scanned. Therefore, the term area result is expressed as mass of bone mineral per unit area scanned (g/cm^2) (3).

The physiologic information provided by measurements of bone mineral content (BMC) has been under extensive investigation during the past 20 years. Bone mass measurements have been a valuable research tool for clinical investigations attempting to elucidate the pathogenesis of metabolic bone diseases. Investigators have sought to determine the clinical significance of bone loss with aging and bone disease and its relationship to an increasing risk of fractures among the elderly. This growing interest in

better understanding the nature and degree of changes in BMC with age, with osteoporosis, and with metabolic bone disease in general has prompted the development of noninvasive measurement techniques for bone mineral density as a function of bone mineral content (4). A variety of such techniques are presently available. They include: radiogrammetry, photodensitometry, radiographic absorptiometry, single photon absorptiometry, computed tomography, and dual photon absorptiometry. These techniques for measuring bone mineral density are designed to assess bone mass. Their main application has been in diseases characterized by bone loss, which results from a number of defined disease processes, such as idiopathic osteoporosis, endocrine diseases, renal diseases, immobilization, and use of certain drugs such as corticosteroids and anticonvulsive drugs (5). Metabolic bone diseases, such as severe renal disease and hyperparathyroidism produce rapid bone loss. Changes of 20 to 30 percent in bone mineral content are possible in a short time. According to Wahner et al., these diseases rarely need quantification of bone loss by sophisticated techniques. For clinical patient management the evaluation of radiographs is generally sufficient (5).

Bone loss also occurs as a pathophysiologic process with aging. Although techniques of measuring bone mineral may assess the presence and degree of osteopenia, they give no information regarding the cause or mechanism of the loss. Many of these methods of bone mass quantitation in general and DPA in particular have been used in attempts to diagnose osteoporosis or to follow its response to therapy. The purpose of this report is to assess the safety and the effect of DPA bone mineral density measurements on the clinical outcome of these patients. This assessment seeks to ascertain where BMD evaluation by DPA fits into the overall scheme of bone disease prevention, diagnosis, and treatment. Other noninvasive measurement techniques for bone mineral will be assessed in separate reports.

BACKGROUND

Historical

In the 1960's standard radiographs were used in the early research attempts to measure BMD. One method, photodensitometry, was used to estimate bone mass by measuring the optical density of bone on x-ray films obtained under standardized conditions (6). The optical density of a radiographic image of bone is roughly proportional to the mineral mass of the exposed bone. The measurements on the film are made with a densitometer. Calibration of each film is accomplished by simultaneous exposure of a reference wedge. Photodensitometry, however, has technical problems relating to the radiographic technique (beam hardening, scattered radiation) and methods of film processing that limit its use (2). The photodensitometric method does not compensate adequately for factors such as soft-tissue thickness (7). Sensitivity to soft-tissue thickness restricts the application of photodensitometry to appendicular bones, particularly the phalanges.

Radiogrammetry (radiographic morphometry) is another method which uses standard radiographs to evaluate BMD. First introduced in 1960, this simple radiographic method measures the thickness of the cortex of metacarpal bones or other peripheral tubular bones (8). The most commonly used site is the second metacarpal of the nondominant hand, or several metacarpals from one or both hands (4). Based on the assumption that cortical thickness is a measure of mass, radiogrammetry uses the ratio of cortical to total width as a measure of bone density. Some investigators determine both cortical area and total area because they believe that cortical area correlates better with the amount of bone present than does cortical width. This method has been used extensively and a vast literature on its use is available on normal populations and on patient populations with various diseases. Radiogrammetry is well suited for detecting endosteal and periosteal cortical resorption with relatively good precision. However, no

evaluation of trabecular bone is possible using this method. Increased cortical porosity, which occurs in some diseases and with aging, is not detected. Radiogrammetry is not a good technique for estimating the quantity of trabecular bone in the spine.

An important breakthrough in the in vivo assessment of bone occurred in 1963, when Cameron and Sorenson introduced a low-energy radioisotope (I-125) photon absorptiometric method (9). Single-energy photon absorptiometry measures bone density in the appendicular skeleton. Measurements are usually obtained from the distal or midradius. This technique known as absorptiometry uses monoenergetic radiation passed across the bone, with the changes in beam intensity being recorded by a nuclear counting instrument (10). Like radiogrammetry, single photon absorptiometry (SPA) is applicable only to appendicular bones because tissue composition surrounding the bone has to be uniform and minimal. As in radiometric techniques (and in contrast to radiogrammetry), cortical and trabecular bone components are not separated, and the entire bone is measured at a cross-section (1). SPA has received extensive use in biomedical research on bone. In the late 1960's, investigators attempting to provide a means of measuring the peripheral skeleton without the necessity of embedding the limb in a layer of tissue-equivalent material, developed the method of DPA. With this new method, investigators also hoped to confront the significant clinical problem of fractures of the spine and proximal femur associated with osteoporosis. Believing that a direct measurement of bone mineral mass of the spine or hip would be clinically useful in addressing this problem, they sought to utilize the DPA method to measure the amount of bone mineral at these sites. With further development of DPA in the 1970's it became possible to measure bone mineral in the axial skeleton, particularly the lumbar spine and hips (11, 12). In the spine, the L2 to L4 region is usually measured because of the homogeneity of bone densities in these vertebrae and the absence of fractures (13). For the hip, bone mineral content is usually calculated from the femoral neck (cervical) and trochanteric regions.

Basic Principles of DPA

DPA is a modification of the single-energy technique using a radioisotope (Gd-153) that emits photons at two different energy levels. Dual photon absorptiometers reduce the effect of soft tissue on the absorption measurements in a two-component system consisting of soft-tissue and bone (13). Because of the different energy dependence of the gamma ray absorption coefficients in bone and soft tissue, dual-photon absorptiometers are capable of correcting for layers of fat and soft tissue overlying the bone. This permits the determination of the density of bone present, independent of the amount of soft tissue (11,14). This point will be addressed in greater detail in a subsequent section on precision and accuracy.

A typical dual photon bone mineral analyzer consists of a rectilinear scanner frame, a 1.0Curie (Ci) Gd-153 source, and a NaI (T1) scintillation detector (1). The system is interfaced with a computer that controls scanning pattern, speed, bone edge detection, data acquisition and other factors. To measure local areas of the axial skeleton, the radionuclide source is coupled to the collimated scintillation detector on a rigid yoke which moves in a rectilinear scanning mode across the spine or hips (1). The instruments are standardized with ashed bones or bone equivalent solutions in specially designed phantoms. Quality control phantoms are supplied and need to be used daily. In the measurement of bone mineral density the anatomic region of interest is scanned and a point-by-point determination of bone mineral is made. The transmission scan is obtained by counting the 42-keV and 100-keV gamma rays of Gd-153 after they have been attenuated by bone and soft tissue (12). The total bone mass is determined by summing the individual point values. The difference in photon absorption between bone and soft tissue allows for the calculation of the total BMC found in the scan path. BMC is inversely related to the measured transmission count rate (2). Using DPA, the bone

minera density measured reflects the total integrated mineral (cortical and trabecular) in the path of the beam. The BMD data, acquired during scanning, can be displayed either as a numerical print-out with a character plot or as an intensity modulated image (12).

Costs

DPA scans of the spine or femur take about 30 to 40 minutes and can be performed without specific preparation on any patient able to remain supine for that time. Several DPA instruments are available commercially. The capabilities of these instruments range from calculation of total skeletal calcium using BMD by DPA, to instruments for spine and hip, or spine alone. Costs for these devices range from about $30,000 to 40,000 for a spine scanner to about $65,000 for models capable of total body scanning (costs do not include radioactive source). The 1.0Ci Gd-153 radiation source that is required has a half-life of 242 days. This source will have to be replaced every 12-18 months at a cost of about $7,000 (15). As of June 1986, there were more than 300 facilities in the United States offering DPA. Charges for the procedure range from about $125 to $185 for a lumbar spine scan. If the femur scan is also performed an additional $60-90 is added to the cost (M. Duerst, written communication).

Among the alternative modalities SPA instruments cost $20,000 to $30,000. A typical SPA examination exposes the patient to 2 to 5 mrad of radiation and costs between $50 and $125 (2,16). The analysis software and calibration device (phantom) that are needed to do absorptiometry with a quantitative computed tomography scanner (QCT) can be purchased for $8,000 to $10,000 (17). A QCT examination typically takes less than one-half hour and costs average between $150 and $250, but can cost up to $400 in some settings (2,17). Low-dose QCT has been noted to expose the patient to a peak skin dose of as low as 300 mrad, but the dose can be as much as 500 to 1,000 mren (16).

OSTEOPOROSIS

Definition

Measurements of bone mineral density by DPA are being used extensively in epidemiologic, pathogenic, and therapeutic studies of osteoporosis. As a result of the considerable morbidity, mortality, and expenditures associated with this disease there is growing interest in research regarding its prevention, diagnosis and treatment. Osteoporosis is considered a major underlying cause of bone fractures in postmenopausal women and older persons in general. It (primary osteoporosis) is an age-related disorder characterized by decreased bone mass and by increased susceptibility to fractures in the absence of other recognizable causes of bone loss (18). Nordin believes that a bone is osteoporotic when the volume of tissue per unit volume of anatomic bone (volume/volume ratio) falls below the normal limit in young adults (19). According to Nordin if the value is within the normal range for the age and sex of the subject, "simple osteoporosis" is present. If the value is below the range for the age and sex of the subject, "accelerated osteoporosis" is present. Other investigators such as Riggs and colleagues use "postmenopausal" and "senile" classifications of osteoporosis (20). According to Riggs and colleagues, women with postmenopausal osteoporosis have lost excessive and disproportionate amounts of trabecular bone compared with peers. In contrast, bone loss in "senile osteoporosis" is proportionate for both cortical and trabecular bone and is only slightly more for patients with, than for those without, fracture (20).

Although osteoporosis affects all bones, fractures of the spine, wrist, and hip are most common. The risk of developing osteoporosis increases with age and is higher in women than in men, and in whites than in blacks (21). Two broad hypotheses have been proposed for the pathogenesis of primary osteoporosis. The first is that skeletal mass achieved at maturity is the critical determinant for development of clinical osteoporosis later in life (20). An underlying assumption of this theory is that the rate of bone loss is

not significantly increased in persons destined to become osteoporotic. This has been supported by the work of Hansson and Roos and Aloia and coworkers (22,23). Bone loss is considered a normal manifestation of the aging process. The second theory of pathogenesis is that those destined to become osteoporotic have significantly increased rates of bone loss by comparison with age- and sex-matched controls (24). The factors responsible for increased rates of bone loss in affected individuals may be the same as those operative during the aging process but are exaggerated. These two theories are not mutually exclusive, and presently it is not possible to state which one of these variables (bone mass at maturity or subsequent rate of loss) is more important.

Bone is composed of a collagen-rich organic matrix impregnated with minerals, largely calcium and phosphate. Two major forms of bone exist, cortical and trabecular. Cortical or compact bone forms the external envelopes of the skeleton. Trabecular or cancellous bone forms plates that traverse the internal cavities of the skeleton (25). The skeleton is 80 percent cortical bone and 20 percent trabecular bone. The proportions of cortical and trabecular bone vary at different sites. Vertebral bodies contain predominantly trabecular bone while the radius and proximal femur contain various contributions of cortical and trabecular components depending on the exact site analyzed (3). The responses of the two forms of bone to metabolic influences and their susceptibility to fracture appear to differ. Bone undergoes continuous remodeling throughout life in a constant, dynamic turnover consisting of bone formation and bone resorption. Peak bone mass is achieved at about 35 years of age for cortical bone and earlier for trabecular bone (18). Mazess reports that in women cortical bone mass shows a slow decline (3 percent per decade) until age 45 to 50 years and then an accelerated bone diminution (9 percent per decade) until age 75 (26). Similar findings have not been consistently obtained by other independent investigators or in men as compared with women. Cortical bone mass loss then decreases to about 3 to 4 percent per decade. In the same report, Mazess surveyed aging changes in trabecular bone and found that the

weight of evidence indicated decreases of trabecular bone beginning during young adulthood (20-40 years old) in both sexes and proceeding at similar rates (6 to 8 percent per decade) thereafter without evidence of age-dependent acceleration. This finding does not coincide with the assumption of an accelerated loss of trabecular bone after menopause.

Risk Factors

Bone mass is approximately 30 percent higher in men than in women, and approximately 10 percent higher in blacks than in whites. Peak adult bone mass in each person is suggested to be determined by a combination of genetic, mechanical, nutritional and hormonal factors (27). Other less well understood factors may also play a role. In each ethnic or gender group bone mass varies among individuals. After reaching its peak, bone mass declines throughout life because of an imbalance in bone turnover in favor of resorption over formation. The factors that appear to be responsible for age-related bone loss and predispose to osteoporotic fracture may include those that determine bone mass (27) and more. When bone mass is steadily lost the bones become fragile and more susceptible to fracture. As bones lose calcium and protein they may remain the same size but the walls of the cortical bone become thinner and the holes in the trabecular bone become larger (28). These changes in composition greatly weaken the structural integrity of the affected bone. While the exact pathogenesis of osteoporosis is not yet completely understood, low bone mass seems to be central to the disease process. Most of the known risk factors are causally related to the development of low bone mass. However, low bone mass is only one of the factors that is important in the pathogenesis of fracture. Trauma may also be important. Not all individuals with low bone mass will fracture. Some individuals will fracture despite relatively normal bone mass (29). Other diseases of the skeleton, e.g., osteomalacia, may occur with or without osteoporosis and may lead to osteopenia and an increased frequency of fractures. As mentioned above, the degree and frequency of trauma is also an important

determinant and some suggest that the frequency of falls increases as a function of age. Since muscle-wasting also occurs with age, the forces generated by a fall may not be widely distributed and may more easily result in fracture. According to Johnston, prevention of bone loss should lessen the frequency of fractures, but may not entirely eliminate the increased risk of fractures associated with aging (29).

Epidemiologic studies of patients who have fractures as well as studies of age-related bone loss, point to some of the factors that may predispose a person to develop osteoporosis. These studies suggest that the development and progression of primary osteoporosis may be enhanced by a variety of factors that upset the normal balance between bone formation and bone resorption. Some factors may be fortuitous associations commonly found among patients with osteoporosis. Risk factors, in addition to small peak adult bone mass, include estrogen deficiency (related either to aging or to premature menopause), other hormonal imbalances, low calcium intake for prolonged periods of time, or loss of calcium and vitamin deficiencies, or metabolic anomalies (most notably, involving vitamin D or hyperthyroidism) (30,31). Calcium deficiency may be an important risk factor because insufficient calcium intake during skeletal development may lead to a lower than expected skeletal mass at maturity. Calcium deficiency in the postmenopausal woman may lead to more rapid bone loss or less aggressive bone formation. While calcium deficiency is deleterious to bone mass, a number of studies found that calcium alone was ineffective against postmenopausal bone loss or less aggressive bone formation. Other risk factors include sedentary lifestyle (decreased mechanical loading) and alcohol or tobacco use or abuse (32,33). Dietary factors that may be involved in osteoporosis include high caffeine intake, high protein intake, and perhaps high phosphate intake (34). Bone mass and susceptibility to fracture may be at least, partly hereditary. No study has determined that family history of osteoporotic fracture is a risk factor for osteoporotic fractures. A small skeletal frame or leanness and northern European racial extraction also increase one's risk of developing

osteoporosis (35). For postmenopausal women, concurrent medical conditions or drug therapy affecting calcium balance (e.g., hyperthyroidism, corticosteroid therapy, or gastrectomy) are also considered clinical risk factors for osteoporosis. For elderly women, risk factors also include a history of previous fractures, a propensity to fall, and reduced mobility (29).

Prevalence and Incidence

Osteoporosis is a major public health problem. The National Institutes of Health Consensus Development Conference on Osteoporosis held on April 2-4, 1984, reported that osteoporosis may affect between 15 and 20 million Americans (36). More than one million fractures attributable to osteoporosis occur annually in individuals over the age of 45. Twenty-five percent of women over 60 years of age have documented vertebral fractures in association with osteoporosis. As many as 50 percent of women will develop vertebral fractures by age 75. These fractures may develop during routine activities such as bending, lifting, or raising from a chair or bed (36). According to the American College of Obstetricians and Gynecologists, after age 45 there is a marked increase in the incidence of distal forearm fractures (28). By age 60, there are ten times more forearm fractures in women than in men of comparable age. These fractures limit the use of the extremity for 4 to 8 weeks, with long-term disability uncommon. While osteoporosis predisposes to fractures of various bones, hip fractures are the most serious in terms of disability, mortality and aggregate cost. In the United States, it is estimated that more than 200,000 hip fractures occur in elderly women each year with 80 percent found to be related to pre-existing osteoporosis (28). The affected population tends to be advanced in age and the sex distribution less skewed toward females than is the case with vertebral fractures. Acute complications such as hospitalization, depression, and mechanical failure of the surgical procedure are common (36). Most patients fail to

recover normal activity. Hip fractures are fatal in 12 to 20 percent of cases, and precipitate long-term nursing home care for half of those who survive (37,38). Hip fractures pose a significant economic as well as a medical burden.

The economic burden of all age-related fractures is truly great because of the large number of people involved and the expensive and protracted care that is often required. About a fourth of all patients with limb fractures require hospitalization and the mean hospital stay increases from 13.6 days among those aged 25 to 44, to 32.6 days among those older than age 65. Fractures of the proximal femur account for more than half of all days of hospitalization for limb fractures. The cost of the acute care alone for fractures of the proximal femur has been estimated to exceed $1 billion annually in the United States (39). The direct and indirect costs of osteoporosis, including hip fractures, are estimated to be between $3.5 billion and $6.1 billion annually in the United States (36,38).

Treatment

The treatment of osteoporosis in postmenopausal women is considered both from the standpoint of preventive measures (prevention of further bone loss in normal women) and therapy of the patient with established disease and fractures (reversal of bone loss). At present, there is no reliable method to treat or reverse osteoporosis after it has been diagnosed (40). Nevertheless, investigators have recommended a variety of therapeutic regimens. The conservative approach in the management of patients with established osteoporosis and fractures has been the use of calcium with vitamin D supplements and an exercise program. According to Heaney there is a growing body of evidence suggesting that nutritional factors play important roles in age-related bone loss, particularly in the postmenopausal period in women (27). He adds that calcium is the most important of these factors and remains an important nutrient throughout adult life. With the aging population at risk of inadequate availability of calcium because of

low dietary intake and poor gastrointestinal absorption, Heaney recommended that postmenopausal women increase calcium intake to at least 1.5g per day if no estrogens were used. Similar recommendations have been made by Nordin and Johnston et al. (41,42). These recommendations are well above the estimated calcium intake of 500 mg per day in postmenopausal women in the United States and still above the recommended dietary allowance (RDA) of 800 mg per day. According to Nordin some 50 percent of women with clinical osteoporosis have malabsorption of calcium. Nordin treats these patients with small doses (0.25 ug per day) of calcitriol to increase calcium absorption (41).

Because postmenopausal osteoporosis is sometimes associated with low levels of plasma 1,25-dihydroxyvitamin D some investigators add therapeutic doses of vitamin D to the drug regimen (43). Avioli suggested that this approach was incorrect and recommended careful dietary and medical histories and measurements of plasma 1,25-dihydroxyvitamin D3 before vitamin D is added to the therapy. While Avioli reserves vitamin D therapy for patients with osteomalacia, he does recommend the use of diets or supplements, that contain at least 400 to 500 IU of vitamin D, to maintain nutritional adequacy (43). Riggs reported that the use of vitamin D was associated with a substantial incidence of hypercalcemia and hypercalciuria, or both. He also recommended that vitamin D not be included as a component of therapy (44). According to Audran recent reports have suggested that impaired formation of 1,25-dihydroxyvitamin D may play a role in senile osteoporosis (45).

According to Avioli, mobilization of the osteoporotic patient is an essential ingredient of any therapeutic protocol. He reported that moderate physical activity such as leg walk, sideward bends, arm crossing and chair pull in subjects aged 69 to 95 effectively retarded the rate of bone loss (43). Heaney believes that mechanical loading is probably the most important determinant of age-related bone loss and needs to be

maintained at as high a level as possible (27). However, not only does physical activity decline with age, but once the disease is present mechanical loading of the skeleton is even further decreased. Currently, it is not known how much mechanical stress is required, or how long it must be sustained to affect skeletal mass.

Although therapeutic intervention with calcium supplementation and moderate exercise programs represent the least risk to the patient, available evidence suggests, estrogen is more effective in preventing bone loss (32,46). Osteoporotic patients who are less than 10 years postmenopausal are usually offered estrogen replacement therapy (34,41,47,48). This therapy is usually combined with an adequate calcium intake of at least 1.0g of elemental calcium per day (41,47). Preliminary data by Ettinger et al. indicate that it may be possible to manage osteoporotic patients with a replacement dose of estrogen that is half as large (0.3 mg) as that presently recommended (0.625 mg) when the estrogen therapy is combined with high-dose calcium supplementation (1.5 g) (49). Nordin and colleagues reported estrogen therapy significantly reduced bone loss in women with crush fractures (50). According to Johnston and associates, calcium and/or estrogen therapy is probably of value in treating patients with crush fracture osteoporosis because of a slowing of the rate of subsequent bone loss and a reduction in the fracture rate (42). Currently, it has become popular to add progestins to the monthly estrogen regimen (48,25).

For symptomatic osteoporosis the therapeutic management of patients has also included fluorides, vitamin D metabolites, parathyroid hormone, diphosphonates, calcitonin, progestins, and anabolic steroids (34,51,52). These agents are used separately or in combination with calcium and/or estrogen. Some investigators question the value of therapies that only serve to prevent further loss of bone in patients already osteoporotic. They believe other measures are required to increase bone formation rate and improve bone density. Nordin suggests the use of anabolic steroids, Aloia, calcitonin whereas Riggs advises sodium fluoride and calcium therapy (41,51,44,). Only sodium

fluoride, in the presence of adequate calcium, has been shown to lead to increased bone mass and a decreased fracture rate (10,53). This regimen may require the addition of estrogen to achieve this goal. Unfortunately a large fraction of treated patients demonstrate serious side effects and many show little or no response to fluoride treatment. There is currently no way of predicting which patients will respond favorably to therapy (37). Additionally, data suggest that long-term use of fluoride leads to cortical bone loss in some patients which in turn may increase the risk of hip fractures. According to Riggs, several studies, including his own, have found that cortical bone decreases significantly during treatment (44). Perhaps the results of the two 5-year prospective double-blind randomized clinical trials supported by the National Institutes of Health will help determine whether problems with fluoride administration can be resolved.

According to Christiansen, there is no efficacious treatment of osteoporosis once symptoms have appeared (52). Lindsay states that treating established osteoporosis is difficult and emphasis should be placed on preventing further fractures rather than on increasing bone mass. He suggests removing environmental influences and treating health problems that may increase the risk of falls (34). After an extensive review of information regarding osteoporosis and osteoporotic fractures, Cummings and associates concluded, that in the already osteoporotic "elderly," prevention of falls seems to offer the greatest potential for reducing the risk of fractures (32). Because of the multifactorial etiology of osteoporosis many views of its causes, prevention, and treatment have been developed by the various specialties to whom these patients present.

Because there is no satisfactory treatment for established osteoporosis, prevention is especially important. To prevent osteoporosis in the immediate postmenopausal period many investigators recommend that patients alter controllable risk factors and increase

calcium intake. Exercise programs are also recommended. According to Heaney, the goal of prophylactic calcium supplementation and exercise is to achieve the highest possible peak bone mass before old age and to maintain that peak for as long as possible (27). Other researchers also believe that the pathologic effects of osteoporosis can be lessened and often eliminated simply by maintaining an "adequate" dietary intake of calcium throughout life and getting regular exercise (54,55). For preventive care in the young adult woman, Heaney recommends a high calcium intake, regular and vigorous exercise, and the avoidance of excess protein, alcohol, smoking and caffeine (27).

Currently, postmenopausal estrogen therapy appears to be the most effective single method for preventing bone loss and fractures in women (32,46). According to Johnston the strongest evidence available from published studies favors the effectiveness of estrogen, or estrogen/progestin combinations in preventing bone loss (42). Generally, investigators are reluctant to prophylactically treat with estrogens postmenopausal women who show no evidence of bone disease. Some recommend estrogen or estrogen/progestin prophylactic treatment for the high-risk group of women potentially liable to develop osteoporosis (31,52). Treatment is usually recommended to begin as soon as possible after the onset of menopause and to be continued for at least five years and perhaps as long as ten years or more (47). The National Institutes of Health Consensus Development Conference Panel concluded that estrogen replacement therapy and increased calcium intake are the mainstays of prevention and management of osteoporosis (36). The panel also indicated that exercise and nutrition may play an important role as well. It was noted, however, that until more data on risks and benefits are available, physicians and patients may prefer to reserve estrogen therapy for conditions that confer a high risk of developing osteoporosis, such as the occurrence of premature menopause.

In deciding whether estrogen should be administered, risks and benefits of estrogen therapy need to be considered. It has been reported that postmenopausal estrogen

therapy increases the risk of endometrial cancer (25,56). Most recently, the findings of Shapiro and associates suggest that long-term use of conjugated estrogen increases the risk of both localized and widespread endometrial cancer (57). The data also suggest that women who have taken conjugated estrogen for 1 or more years remain at increased risk for at least 10 years after they discontinue use. A similar finding of increased risk of endometrial cancer among users of conjugated estrogens has been reported by Buring and associates. This risk increases with longer use and higher dosages (56). According to Johnston and colleagues, the use of a progestin with the estrogen may reduce the risk of development of carcinoma of the uterus (42). In regard to breast cancer, Cummings and coworkers suggest that most evidence indicates the risk for breast cancer is not increased, although a few positive findings have been reported (32). The use of estrogen also entails the increased cost of medical followup and problems with patient compliance (44).

One potential benefit of estrogen, in addition to reducing bone loss, is the increasing evidence that estrogen therapy might protect against coronary heart disease in women (32). Studies assessing the risk of myocardial infarction and stroke in postmenopausal women taking predominantly unopposed estrogens are equivocal. More research is needed in this area. According to Haber, progestins which have been added to the monthly estrogen regimens to reduce the risk of endometrial cancer may also negate the beneficial effect of estrogen on coronary heart disease (48). In addition to a return of the menses a potential risk of progestin therapy is the increased risk of cardiovascular disease. Haber and other investigators recommend additional studies prior to the widespread and routine use of progestins (32,48).

In the past five years, investigators have used DPA to measure the BMD of the lumbar spine and proximal femur in "normal" individuals and in patients with osteoporosis. Studies have been conducted to investigate whether spine and/or hip bone mineral measurements could separate "normal" women from women with vertebral

compression fractures or femoral neck fractures. Recently, some investigators have used DPA measurements ostensibly to identify women at risk for future fractures. This report examines these and other studies as well as other available evidence that pertains to the safety and clinical effectiveness of this technique.

RATIONALE

The rationale for bone mineral measurements is based on the demonstration that the strength or resistance of a bone to fracture is closely related to the amount of bony tissue or the mass of the mineral present in the bone. Proponents argue that since the (breaking) tensile strength of bone is related to its mineral content, measurements of BMC at the actual sites of fracture should be the most accurate method of determining fracture risk. Proponents of DPA believe that the ability to determine accurately the direction and degree of changes in bone mineral density as a function of bone mineral content in the spine and proximal femur (sites of fracture) facilitates the diagnosis and management of metabolic bone diseases, such as osteoporosis. They argue that information on bone mineral loss is clinically important for the monitoring of age-related bone loss, for the diagnosis and monitoring of bone loss resulting from metabolic bone disease, for the assessment of drug effects on bone mineralization, and for the accurate assessment of fracture risk at specific bone sites (spine, femoral neck). Proponents also argue that these measurements could prove useful as clinical guides to therapy in assessing the therapeutic responses of patients with osteopenia.

REVIEW OF AVAILABLE INFORMATION

Accuracy and Precision

To determine the accuracy of DPA diagnostic tests, the measurement is compared with some independent measurement of bone mass, such as ash weight or physical density (58). Accuracy defines the degree to which a measurement, or an estimate based on measurements, represents the true value of the attribute that is being measured. In the determination of osteopenia, accuracy in the measurement of bone mass by DPA is of great importance.

A number of complex technical factors affect dual photon accuracy determinations in vivo. These necessitate corrections for deadtime of the counting system, beam hardening, and scattered radiation (59). When these corrections are made, measurements on bone phantoms (phantoms with known concentrations of dipotassium hydrogen phosphate solutions) have shown excellent accuracy. However, differences in laboratory practices can lead to variable results (7). The accuracy of DPA determined by Wilson and Madsen in bone phantoms was 1.2 percent (standard error of estimate) (11). Krolner and Pors Nielsen reported 1.3 percent (14). According to Mazess the accuracy error for DPA is 3 to 5 percent on actual vertebral or femoral specimens scanned under in vivo conditions (59). Genant reported 4 to 10 percent (60). Genant and associates believe that vertebral compressions, hypertrophy of articular facets, discogenic sclerosis or marginal osteophytosis and extra-osseous calcification, which are widespread in the elderly and are included in the integral measurements of DPA, may result in inaccurate as well as poorly reproducible vertebral measurements (61). Cohn reported that the accuracy of the DPA method (greater than 5 percent) is markedly reduced when the technique is used for measurement of the spinal column bone or any irregularly shaped bone surrounded by a large volume of tissue (62). He found systematic measurement

errors introduced by variation in the distribution of fat in the bone, and by the variable size and shape of the vertebrae, particularly after the vertebrae have been altered by a crush fracture.

Initial work by Wilson and Madsen (1977) and Krolner and Pors Nielsen (1980) showed that accurate results could be obtained regardless of soft tissue thickness or composition (11,14). It was shown that the influence of fat on the measured bone mineral would be negligible if the fat layer over the vertebrae had the same thickness as the fat layer over the site used for baseline measurements (14). However, a nonhomogeneous distribution of adipose tissue in the body areas transversed by the scanning radiation beam may lead to an underestimation or overestimation of BMC. Roos and associates, have found that fat in the adipose capsules of the kidneys may cause an overestimation of the bone mineral content in the third lumbar vertebra by DPA (63). Krolner and Pors Nielsen reported that a nonuniform increase in fat surrounding the lumbar spine may show a decrease of bone mineral density measurements (14). DPA attenuation equations assume that soft tissue is homogeneous, whereas in practice it consists of variable amounts of fat. Variations in fat-lean composition produce differences in the attenuation coefficients for soft tissue that influence measurements which may lead to erroneous results (14,64) According to Tothill, investigators have ignored the errors introduced by this factor (65). Mazess reported, however, that there is little influence of nonuniform tissue composition on bone, as might occur if composition above the spine differs from that surrounding it or if fat composition of the marrow varies (7). He reported that the variation in density measurements due to a 3 percent shift of fat is virtually undetectable. Recently, Wahner and colleagues have also reported on the effect of fat on DPA bone mineral density measurements (66). According to the investigators, bone mineral density measurements may be affected by changes in body

fat, such as a nonuniform increase in fat surrounding the lumbar spine. Conversely, they found that changes in intraosseous and intramedullary fat had little effect on the measured bone mineral density (66).

Mazess found that a calcified aorta lying to the side of the spine can cause substantial problems in the soft tissue baseline determinations causing underestimation of bone mass. If the calcified aorta is above the spine the bone mass is overestimated (59). According to Mazess the use of an improper or average baseline can cause errors of 20 percent or more in bone determination. Because a soft tissue baseline can vary by 5 to 10 percent, Mazess recommends determining the soft tissue baseline along the entire length of the lumbar spine for accurate bone determinations (59). He identified the ribs, calcified aorta, transverse processes, and even the iliac crest as factors that could adversely affect baseline measurements. Mazess reported that incorporation of data from these locations into the soft tissue baseline measurement erroneously elevates the baseline and reduces the apparent BMC (59).

For monitoring changes in bone mass, DPA bone mineral measurements have to be sufficiently precise (reproducible) to provide an accurate estimate of these changes. The coefficient of variation, expressed in percent, describes how precise or repeatable a given measurement is. Several investigators have reported the in vivo precision of DPA to be better than 3 percent (coefficient of variation) (11,12,67). Krolner and Pors Nielsen found the coefficient of variation of repeated measurements ranges from 1.4 percent in normal premenopausal women to 2.6 percent in postmenopausal women with clinical osteoporosis (14). They suggest that the smallest significantly detectable difference in the women measured would be a BMD change of 4 percent in normal premenopausal women and 7.4 percent in postmenopausal women with clinical osteoporosis.

Because the clinical usefulness of bone mineral measurements depends on the long-term reproducibility of the applied method in vivo, Krolner and Pors Nielsen performed

long-term precision measurements of the BMD of the lumbar vertebrae utilizing DPA (68). In this study the BMD measurements were taken at 6- and 31-month intervals rather than the 14-day interval used in their earlier study. The authors concluded that the long-term reproducibility of DPA measurements in vivo must be based on measurements in vitro because of changes in lumbar BMC and fat distribution. From in vitro measurements they calculated a coefficient of variation of 1.4 to 2.5 percent in the BMD range of normal premenopausal women, and 2.0 to 7.9 percent in the BMD range of osteoporotic women with vertebral compression fractures (68). According to Mazess, the major problems for clinical use of DPA involve the precise and reproducible location of the measurement site (59). In the lumbar spine, poor spatial resolution and crush fractures can lead to uncertainties of positioning. To obtain maximum precision, LeBlanc and colleagues found that a previous scan must be compared directly with the current one (69). This was demonstrated by analyzing scans integrating a region intentionally shifted three lines above the originally chosen lines. Failure to compare the same area resulted in an additional error of 2 to 4 percent.

In this recent study, LeBlanc investigated the precision of two dual photon absorptiometers using scans of phantoms, normal subjects, and patients (69). He found phantom measurements for one instrument 2 to 5 percent lower than for the other. Moreover, the auto and manual methods of analysis gave significantly different BMD values for both instruments, with the manual method having better precision. According to LeBlanc, the manual/auto BMD differences result from a difference in edge selection. The automatic method used by the computer determined values for bone edges and baseline while the manual method involved a line-by-line inspection of edges and baseline. The author suggests that changes in analysis software might improve the automatic edge detection and therefore improve precision in this mode (69).

LeBlanc and colleagues determined that the average BMD percent precision error of the two instruments was 4 percent at a 95 percent confidence level (69). These

findings indicate that to be confident (95 percent) that a real change had occurred in BMC, two scans would have to differ by more than 5.6 percent. The authors also found, contrary to popular belief, that for observers with similar training interobserver analysis error was essentially equal to the intraobserver error.

Preliminary results from a study of bone mass in 50 postmenopausal osteoporotic women at the University of Washington was recently reported by Chesnut at the National Institutes of Health Consensus Development Conference on Osteoporosis (36). With DPA measurements of the spine, he reported obtaining a precision of 3 to 5 percent and an accuracy of 2 to 4 percent. Similar values for precision were obtained for DPA measurements of the femur. The accuracy of the femur measurements was not provided. These results were obtained with modifications made by the group at the University of Washington to the DPA scanner that resulted in scanning images that clearly delineated the vertebral bodies. According to Wahner and associates, part of the problem inherent in assessing the accuracy of DPA is associated with the determination of anatomic areas corresponding to the scanned areas (spatial resolution) on the highly variable vertebrae (70). Wahner and coworkers compared the BMD of 26 L2-L4 segments, removed from cadavers, and measured by DPA, with the area density determined from an ashed specimen of L3. They reported an error of about 5 to 6 percent in determining BMD in excised vertebrae with DPA. On the more uniform femoral neck they were able to obtain an accuracy of 3 to 4 percent with DPA (70).

Because relatively few longitudinal clinical studies have been performed to date utilizing DPA, little information is available regarding the effects of the Gd-153 source decay upon soft tissue correction. According to Pors Nielsen and Krolner the precision in vitro of the DPA method depends on the activity of the radioactive source (71). They found the coefficient of variation became two to three time higher when the radioactive source decayed from 1.2 to 0.4 Ci. Other problems regarding the radioactive source have

been reported. According to Wasnich and Vogel (written communication) the current algorithm for DPA does not correct appropriately for soft tissue effect as the Gd-153 source decays. However, this has not been reported by other investigators.

Bone Mass/Bone Strength

In osteoporosis, bone is decreased in amount, i.e., the bone mass is decreased per given volume. The bone cortex is thin. The trabeculae are decreased in number and size, increasing bone "porosity" and decreasing its tensile and compression strength (load-bearing capacity). Bone fracture represents the overriding clinical consequence of osteoporosis. When the skeleton is exposed to physiologic forces or to trauma, regions of it are subject to exceedingly great stresses. Fractures occur when the local stresses exceed the tensile and/or compressive strength of bone in that region (72). The relationship of bone strength and resistance to fracture to the quantity of bone (mass) had been studied in vitro by many investigators. In 1977 Martin and Atkinson reported on a study of 37 normal femoral specimens that determined the age- and sex-related changes in the structure and strength of the human femoral shaft (73). They observed that while the material strength of femoral bone decreases with aging for both sexes, the moment of inertia (second moments of area) of this structure increases for males but decreases for females. According to Martin and Atkinson, in males the increased moment of inertia compensates for the decline in material strength, whereas in females the diminution in both is additive and contributes to skeletal weakness (73). The investigators found that the male and female mean bone diameters did not reflect the differences in the moments of inertia observed between the sexes. Because the moment of inertia depends on the fourth power of the diameter only slight changes in the linear dimensions of the bone are needed to produce large differences in the moments of inertia

and structural strength. The authors observed a tendency for the endosteal or inside diameter in the female femoral sections to increase and the cortical thickness to decrease with age (73).

In a similar in vitro study, Wall and associates reported that both density and intrinsic strength of femoral bone increase up to about the fourth decade of life and then decrease with age (74). They noted that the rate of decrease of strength is greater than that of density. Strength decrease from the fourth to the eighth decade of life was about 20 percent, whereas the corresponding density decrease was only about 2.6 percent (74). According to Wall the data indicated that either strength is extremely sensitive to any change in the denisty of bone or other factors may play an important role in determining strength of bone. Some studies of the relation between compression strength of the vertebrae in relation to age suggest that strength increases with age until 30 years of age and thereafter decreases, with an appreciable drop after 50 (75).

When it became possible to determine in vivo the BMC as a function of BMD of separate vertebrae of the lumbar spine by DPA, studies were initiated to correlate BMD values and ultimate compressive strength of lumbar vertebrae. It was hoped that these measurements would provide a basis for estimations of normal and abnormal amounts of bone mineral in the vertebrae and to predict patient susceptibility to fracture. In 1980 Hansson and coworkers used DPA (Am-241/Cs-137) to measure the BMD of 109 lumbar vertebrae from 36 different autopsy subjects; mean age 59 years (76). After determination of the BMD, the ultimate compressive strength was determined by compression of the vertebral body until fracture occurred. The authors reported a statistically significant positive correlation between the BMD of all 109 lumbar vertebrae and the compressive load needed to cause a fracture ($R=0.86$, P less than 0.01). Similar findings of mineral content that were highly correlated with resistance to compressive forces had been reported by Bell and colleagues for the vertebrae, and Dalen and associates in the femoral neck (77,78). Interestingly, in the study by Hansson the

posterior elements were not included when the vertebral bodies were compressed. According to the authors these parts of the vertebrae carry an almost negligible share of the axial load. However, the posterior elements and the vertebral bodies added almost equal proportions to the total BMD measured by DPA (76).

The findings of Hansson and colleagues suggested that BMD measurements of the lumbar vertebrae by DPA could be used as an indirect measure of ultimate compresssive strength (76). However, their findings of a linear correlation between the BMD (g/cm^2) of lumbar vertebrae and the ultimate compressive strength of their vertebral bodies is in disagreement with the findings of Bell and associates and Carter and Hayes (77,79). The findings of these investigators indicated that the compressive strength of bone is related to the square of the apparent density. Based on this relationship, which is similar to the findings of the earlier in vitro studies, small changes in apparent bone density can generate large changes in strength. Apparent density, expressed in g/cm^3, is the mass of bone tissue divided by the bulk volume of the test specimen, including mineralized bone and bone marrow spaces.

According to Ruff and Hayes, one structural variable that is not often considered in studies of skeletal aging of long bones is the global geometry of cortical bone (80). The investigators believe that the geometric distribution of bone tissue, together with its material properties, is critical in determining the structural strength and rigidity of the whole bone. To demonstrate this concept the investigators studied cortical bone remodeling with aging in femoral and tibial cross-sections obtained from an archeological collection (81). This Pecos Pueblo collection represents a large, late, prehistoric and protohistoric site in New Mexico. Ruff and Hayes observed increases with age in subperiosteal dimensions and second moments of area in both males and females. However, they also found that this remodeling process is modified by localized bone site differences in mechanical loadings, some of which are apparently sex-specific (81). According to Ruff and Hayes, regions, male or female, subjected to relatively high

mechanical stress in vivo would show the greatest increases with age in total subperiosteal area and second moments of area and the smallest decreases in compact cortical bone area. Conversely, regions with relatively less mechanical stimulation would show small increases (or actual decreases) in subperiosteal apposition of bone and second moments of area. Ruff and Hayes concluded that exercise-related apposition of bone on the subperiosteal surface may mechanically compensate for endosteal resorption and cortical thinning with aging, and reduce the risk of fracture among those individuals (male or female).

The authors believe that a difference in activity levels between their sample population and that of the Martin and Atkinson study could explain the difference in their findings (81). They suggest that the lifestyle of Pecos females subjected them to significantly more strenuous exercise than females from modern industrialized populations, the source of subjects for the Martin and Atkinson study. According to Ruff and Hayes these generally higher levels of activity could account for the greater apposition of bone throughout life among Pecos females (81). Chalmers and Ho cited greater physical activity as a contributing factor to the lower rate of hip fractures among the elderly, particularly women, in nonindustrialized as compared to Western industrialized populations (82).

The relative contribution of trabecular bone and the cortial shell to the load-bearing capacity of the vertebra has been the subject of much controversy. Because DPA provides an integrated measure of both cortical (30-40 percent) and trabecular contributions to mineral content, the contribution of the cortical shell to the load-bearing capacity of the vertebra is of extreme importance to the significance of the DPA measurements. This is especially true in light of the recent findings of Hayes and Gerhart that the cortical shell contributes very little to the overall strength of the vertebral body (72). Their work supports the earlier findings of Bell that the compression strength of the vertebrae depends almost entirely on the trabeculae, which form a three-

dimensional grid within the body (77). These findings, however, were not consistent with the observations of Rockoff and colleagues who reported that the cortical shell contributed 45-75 percent of the peak strength (83).

Clinical Applications

Spine. Investigators after initiating clinical studies established the feasibility of the DPA technique to measure bone mass at the spine and proximal femur. At the Mayo Clinic Riggs and associates studied the effectiveness of DPA to differentiate patients with idiopathic spinal osteoporosis (presence of nontraumatic compression fractures) from normal subjects (3). In that cross-sectional study reported in 1981, DPA was tested in a population of 105 normal women and 76 women patients with osteoporosis. Bone diminution with aging was assessed by measuring BMD concurrently at sites in the axial and the appendicular skeleton. BMC of the spine was assessed from scans of the L1 to L4 region. The BMD value included vertebral bodies and disk interspaces.

In normal women the authors found that vertebral bone loss began in young adulthood and continued linearly throughout life. In contrast to the findings in the appendicular skeleton there was no demonstration of an accelerated bone loss due to the menopause. The cumulative diminution of BMD from the vertebrae throughout life was 47 percent. Riggs and coworkers found that patients with osteoporosis had significantly lower mean BMD values at the vertebrae (p less than 0.001) compared with age comparable normal subjects. However, although the spinal measurements gave the best discrimination of osteoporotic patients from normal subjects there was still considerable overlap between the two groups (3).

To define spinal osteoporosis in terms of vertebral BMD rather than the presence of nontraumatic vertebral fractures the authors arbitrarily chose the 90th percentile for vertebral BMD for patients with nontraumatic vertebral fractures. This value, 0.965 g/cm^2 was then defined as the threshold below which the risk for nontraumatic vertebral

fractures increases. However, with this approach, by age 65 years, half of the women, and by age 85 years, virtually all of the women in the normal female population have BMD values below the threshold for fracture. All these women would be considered to have asymptomatic osteoporosis by the authors (3).

According to Riggs, the results of the study indicated that women with and without spinal osteoporosis lose substantial but similar amounts of cortical bone, but those with spinal osteoporosis lose more trabecular bone. The authors suggested that cortical bone and trabecular bone function as separate compartments which differ in respect to onset and rate of bone loss and possibly also in respect to homeostatic regulation. They believe that direct spinal measurements of bone density are greatly superior to appendicular measurements for evaluating the severity of spinal osteoporosis (3). However, because the lack of response of vertebral bone loss to menopause with DPA measurements was not consistent with the results of other studies, Riggs recommended that the effect of the menopause on the rate of bone loss in the vertebrae relative to that in the appendicular skeleton be studied further. Meunier and colleagues in a histological study of trabecular bone mass in iliac biopsy specimens from 236 control subjects found an acceleration of the linear diminution of trabecular bone as age increased in the postmenopausal period (84). Genant and associates reported a similar acceleration in bone loss at menopause in their study of vertebral mineral determination by quantitative computed tomography (85). According to the authors, the rate of integral spinal bone loss assessed by QCT is roughly one-half that of purely cancellous bone and may explain the difference in sensitivity with DPA. However, Krolner and Pors Nielsen assessed vertebral bone loss by DPA in a longitudinal study of 59 normal women and found an accelerated bone loss of nearly 6 percent immediately after the menopause (86).

Mazess proposed that the common assumption about a large ongoing loss of trabecular bone after menopause may be erroneous (26). He does not believe that the bases for assuming a disproportionate effect of estrogen on trabecular bone is well

supported. For example, he suggests that the apparent rapid loss of trabecular bone observed in the spine with quantitative computed tomography may be an overestimate due to the influence of an increasing fat content (26). According to Mazess, fractures of the vertebra and distal radius, which occur earliest in postmenopausal women, may be due to a trabecular bone loss that has a much earlier onset than that of compact bone loss and not to a more rapid rate of loss of trabecular bone. In contradistinction, the results of the recent study by Richelson and associates (1984) indicated that estrogen deficiency was the predominant cause of bone loss occurring during the first two decades after natural menopause (87). In that study DPA was used to determine the BMD at the femoral neck, femoral intertrochanter, and lumbar spine in 14 women who had undergone oophorectomy during young adulthood, in 14 normal perimenopausal women, and in 14 normal postmenopausal women.

Similar results were reported in an earlier study by Lindquist and associates (1981) on the influence of aging and menopause on BMC based on BMD measurements (88). In that cross-sectional study, bone density was determined in the third lumbar vertebra in a random sample of women by the DPA technique. The authors chose the ages of postmenopausal times in such a way as to make it possible to compare women of different ages but of similar menstrual status and women of different menstrual status but of similar age. According to the authors the results of the study support the hypothesis that there is an association between early menopause and accelerated bone loss (88). A 5-year longitudinal followup study by Lindquist and associates has confirmed the results of their previous cross-sectional study (89). When the same women had lumbar spine BMD determinations with DPA 5 years later the authors found larger differences in BMC between women of different menstrual status than between women of different ages. As in the cross-sectional study, the results from the longitudinal

followup indicated that the time of the menopause influences bone density, with significantly (p less than 0.01) lower values in those women who have an early menopause (89).

In a more recent longitudinal densitometric study, Riggs and coworkers found that vertebral loss in 139 normal women began well before menopause (90). Riggs measuring BMD at the lunbar spine for up to 3 years by DPA found continuous bone loss over adult life with a mean rate of loss of 1.2 percent per year. Moreover, rates of loss were similar in premenopausal and postmenopausal women. From this new data, Riggs concluded that the experimental design of the Richelson study, discussed above, was inadequate because the perimenopausal control group had already undergone substantial bone loss before menopause (90). He also suggested that oophorectomy might induce greater bone loss in young women in whom bone turnover is more active than in older women.

According to Riggs and coworkers there is a striking difference in the patterns of appendicular and axial bone loss in women throughout life (90). They confirmed only a small amount of cortical bone loss in the appendicular skeleton before menopause, with large amounts lost thereafter. By contrast, their longitudinal studies show vertebral bone loss begins well before menopause and continues linearly into old age with only a trend toward midlife acceleration.

Aloia and coworkers recently used DPA measurements of the spine in healthy women and women with vertebral crush fracture syndrome in their cross-sectional study of involutional bone loss (23). In contrast to the findings by Riggs and colleagues, Aloia determined that the best fit for the rate of involutional bone loss from the spine based on cross-sectional data was a two component curve. This indicated an accelerated loss of bone from the spine after menopause. Based on the available information, including published prospective data, Aloia concluded that there is an accelerated loss of bone from the spine after menopause (23).

In addition to the DPA measurements of the lumbar spine, the study by Aloia also included measurements of bone mass of the total skeleton and distal radius by in vivo neutron activation analysis, and SPA, respectively (23). The author found that the spinal measurements did not separate patients with osteoporosis from controls any better than the other bone mineral measurements. According to Aloia, although spinal bone mineral measurements could correctly classify about 77 percent of the cases, the number of misclassifications in the older age group of the normal women was substantial. Moreover, the bone mass measurements of the total skeleton, distal radius and spine determined by Aloia do not support the hypothesis of Riggs and colleagues (38) that women with vertebral crush fractures have preferential loss of spinal bone (23). According to Krolner the lumbar BMD of patients with only one vertebral fracture is less than 1.0 standard deviation (SD) below the age-matched normal mean (91). He suggests that women having their first spinal wedge fracture are indistinguishable from their normal peers as to the total bone mass of the lumbar vertebrae. Accelerated osteopenia of women having multiple vertebral fractures might be a consequence (immobilization) rather than a cause of fractures (91).

Other investigators have also used the DPA technique to measure the BMD of the spine and hip in populations of normal women and women with clinical osteoporosis. The technique was used by Schaadt and Bohr when they studied changes in BMD in the lumbar spine, femoral neck and femoral shaft in normal aging women, prednisone treated women, and in women with primary osteoporosis (92). Acccording to the authors the mean lumbar BMC measured by BMD of 19 women with primary osteoporosis was 31 percent lower than that of 36 postmenopausal age-matched controls. Bone mineral diminution in the femoral neck, which consists of a mixture of trabecular and cortical bone, was smaller than that of the lumbar spine but greater than that of the middle of the femoral shaft which consists of predominantly cortical bone. Schaadt and Bohr observed the same patterns of bone mineral loss in normal aging women and prednisone-

treated women. According to Schaadt and Bohr, the study demonstrated that in postmenopausal women and in the development of osteopenia, the loss of trabecular bone mineral is much greater than cortical bone loss. They suggested that direct measurement of BMC in the lumbar spine was necessary for an accurate evaluation of bone mineral status in that clinically important region (92).

In the Danish study by Krolner and Pors Nielsen, referred to earlier, the authors used DPA measurements of the spine in an attempt to differentiate women with spontaneous vertebral compression fractures or femoral neck fractures from normal women (86). The bone mass measurements were also to be used to identify women at risk of future fractures. BMD of the second, third, and fourth lumbar vertebrae was determined in normal women and women with clinical osteoporosis by using DPA in cross-sectional and longitudinal studies. According to Krolner and Pors Nielsen, the mean lumbar BMC of 86 women (aged 58-89 years) with primary osteoporosis was 41 percent lower than that of normal premenopausal women and 18 percent lower than that of age-matched controls. Nevertheless, the data showed, as did the data of Riggs (3), a large overlap between patients with clinical spinal osteoporosis and age-matched normals (86). The overlap is so large that the majority of patients with clinical spinal osteoporosis are indistinguishable from age-matched normals. Mazess reported that a very large overlap in the spinal density of fracture and nonfracture cases can be expected (93). Recently, he reported that about 60 percent of fractured lumbar vertebrae are entirely normal in density (94).

Krolner and Pors Nielson suggested that a difference in the duration (approximately 3 years) of accelerated bone loss in a subgroup of postmenopausal women in the early menopause could explain the 18 percent difference in lumbar BMC between patients and age-matched normals reported in their study. Krolner and Pors Nielsen point out that while the occurrence of vertebral compression fractures is related to bone mass, the significance of this quantitative approach in vivo remains uncertain. For example, a

minor loss of transverse trabeculae within the vertebrae that is barely detectable with the DPA method could contribute considerably to the weakening of the bone. The authors noted that arteriosclerosis of the lumbar aorta may account for nearly 15 percent of the measured BMD in severe osteopenia and give erroneously high values (86). In contrast, as noted by Cummings, the inclusion by Krolner and Pors Nielsen of subjects with nontoxic goiters, who might be on high doses of thyroid hormone, in the control population could result in erroneously low spinal bone density measurements for the control group (95).

In 1982, Krolner and associates reported on an investigation in a consecutive series of 132 women with and without osteopenia in whom radiography and DPA were compared (96). The investigators hoped to determine if a correlation existed between the two methods and if the loss of vertebral bone mass is concealed by the addition of bone mineral in nonrelevant structures such as the vertebral processes, osteophytes, and calcifications of the abdominal aorta. According to Krolner, the radiographic grade of osteopenia and the BMD of the lumbar vertebrae showed a significant inverse correlation. Each grade of radiographic osteopenia was associated with a large scatter in lumbar BMD. The overlap between normals and patients with obvious osteoporosis comprised nearly 60 percent of the cases with compression fractures. The data also suggested a considerable overestimation of the true vertebral bone mass when DPA was used in patients with osteophytes and severe aortic calcification. The authors found that spondylosis (osteophyte formation) accounted for 10 to 35 percent of the lumbar BMD measured in women with radiographically proven osteopenia. In severe osteopenia aortic calcification may account for nearly 10 percent of lumbar BMD (96).

Seeman and associates compared DPA BMD values of the lumbar spine to SPA BMD values for the radius in 100 patients with various types of endocrine dysfunction (97). The authors found that BMD in each endocrine disorder deviated in at least one site from the sex-specific age regression of 187 normal subjects. BMD measurements indicated

bone loss for patients with primary hyperparathyroidism, hypercortisolism, and hyperthyroidism. For patients with secondary hyperparathyroidism due to chronic renal failure, acromegaly, and postsurgical hypoparathyroidism the BMD measurements suggested bone gain. With the use of multivariate analyses of variance the authors found significant differences in the BMD measurements among the scanning sites. Seeman concluded that bone density of the appendicular and axial skeleton changes differentially in response to endocrine dysfunction and these changes are both site and disease specific. According to the authors, BMD measurements in the appendicular skeleton do not reliably predict BMD measurements of the lumbar spine. BMD changes induced by an endocrine or metabolic disorder mandate assessment of both the appendicular and the axial skeleton (97) Ott and coworkers have also suggested that in postmenopausal osteoporosis the bone may display different rates of change at different sites (98). Because the rate of change may be influenced by the relative amount of trabecular bone, the axial skeleton may not change at the same rate as the appendicular skeleton.

Ott studied longitudinal changes in bone mass after 1 year by DPA and other noninvasive measurement techniques in patients with osteoporosis (98). She found that in these women there were no correlations between measurements of 1-year changes in bone mass by the various techniques. In addition to the possibility of different rates of bone changes at different sites of the skeleton, Ott suggests that the lack of correlation between the measurements may be related to the precision of the techniques and the magnitude of the changes in bone in osteoporosis. She concluded that the techniques used (DPA, CT, SPA) were not sufficiently precise to measure the small amount of change in bone after only 1 year (98). Similar findings for DPA have been reported by Cohn, Krolner, and Cummings and Black (62,91,99). According to Riggs and Melton DPA measurements every 6 months over 2 to 3 years are required to estimate individual rates of bone loss (90).

Ott found that the precision of the DPA and CT techniques was lower in her

clinical setting than in some reports from the literature (98). Several factors probably contribute to this discrepancy. According to Cummings and Black scans obtained in carefully controlled research environments might have better reproducibility than scans obtained in other clinical settings (99). Also, claims of greatest precision are often based on repeated measurements of phantoms or bone specimens, or measurements in persons that are repeated within a short time. Persons cannot be repositioned or kept in position as well as phantoms or specimens (99). The study by Ott indicates that when these techniques for measuring bone mineral, including DPA, are applied to persons (more so to osteoporotics) in clinical settings over long periods of followup, the reproducibility is likely to be poorer than has been reported from specialized research centers (99).

Hip. In 1982 Riggs and associates reported the results of another cross-sectional study where DPA was used to assess changes in BMD with aging (20). They studied the effectiveness of DPA to differentiate patients with hip fracture from normal subjects by measuring changes in the BMD of the proximal femur and spine with aging in 123 normal women and 26 women with hip fractures. In normal women, BMD declined linearly during life by 58 percent in the femoral neck and 53 percent in the intertrochanteric region of the femur. By age 75 years, the authors found that virtually the entire population of aging women had BMD values for the proximal femur that were below their arbitrary threshold for hip fracture. This approach put the entire population of elderly women at risk for hip fracture.

According to Riggs, patients with femoral neck and intertrochanteric fractures were indistinguishable from normal women by differences in BMD at either site (20). Although elderly women with hip fractures had lower values for BMD of the contralateral hip than their peers, the decrease was small and the overlap considerable. For the 26 elderly women with hip fractures, the mean Z-score (deviation in standard deviations from age-adjusted predicted mean) for BMD of the femoral neck was only slightly decreased (-0.50 SD, p less than 0.01), and all individual values were within the age-

adjusted normal range. From these data the authors suggested that although lower BMD of the proximal femur may play a partial role, the occurrence of falls may be a major factor predisposing some but not others in the population of aging women to fracture of the hip (20). This may represent a biased group since Riggs and associates studied ambulatory patients who had survived for at least 1 year after the fracture. According to Cummings, the hip fracture patients chosen for the study may represent a subgroup of otherwise healthy patients who may have had greater bone mass than those who died or were unable to walk (95).

Riggs and colleagues found that the values for BMD of the lumbar spine, midradius, and distal radius sites in the patients with hip fractures did not differ significantly from those for age-comparable normal subjects. By contrast, for 27 additional women ages 51 to 65 years, with nontraumatic vertebral fractures, but not hip fractures, the investigators found a low mean Z-score for BMD of the lumbar spine (-1.92 SD, p less than 0.001). According to Riggs, data from previously published studies and the results of their present study suggest the existence of two distinct osteoporotic syndromes. They designated one form, postmenopausal osteoporosis, characterized by an excessive and disproportionate trabecular bone loss that involves a small subset of women (estimated at 5 to 10 percent) in the early postmenopausal period. It is manifested mainly by vertebral fractures. The other form they designated senile osteoporosis. This syndrome was characterized by a proportionate loss of both cortical and trabecular bone that involves essentially the entire population of aging women (usually older than 75 years) and to a lesser extent, aging men. It is associated with hip fractures or vertebral fractures or both (20). More recently, postmenopausal and senile osteoporosis have been referred to as type I and type II osteoporosis, respectively (100).

Bohr and Schaadt used DPA to determine whether a reduction in BMD of the femoral neck and shaft or of the lumbar spine could be demonstrated in women older than 60 years of age with unilateral fractures of the femoral neck (101). DPA bone

mineral density measurements of the lumbar spine, femoral neck, and femoral shaft in 46 women ranging in age from 60 to 89 years with fractures of the femoral neck were compared with that of 38 healthy women in the same age group. The investigators reported that the BMD of the lumbar spine and femoral neck were not significantly reduced in elderly women with fractures of femoral neck as compared with control subjects. They found the BMD of the femoral shaft, a predominantly cortical bone site, significantly reduced in the fracture group (101). Bohr and Schaadt concluded that the high incidence of femoral neck fracture with increasing age might be explained in part by a reduction in BMC, primarily cortical bone mineral. They added, however, that it is likely that other factors that reduce the strength of bone or increase the tendency in older persons to fall such as dizziness, diminished visual acuity, or muscle weakness, are also of importance (101). In his review of hip fracture studies, Cummings reported that Bohr and Schaadt could have missed a true difference in bone mass because of a small sample size (95). According to Cummings, the study by Bohr and Schaadt may have had insufficient power to detect clinically important differences (type II error).

Cummings studied the role of osteoporosis in the occurrence of hip fractures by critically reviewing case-control studies that have compared the bone mass of patients with hip fractures with that of control subjects (95). He found that the case-control studies suggested that the hips of patients with hip fracture are more osteoporotic than those of other persons of similar age who exhibit no fractures. However, the bone mass differences were usually small and overlapping. While some investigators found patients with hip fractures with substantially less bone at various sites, other investigators have found no significant difference in bone mass between patients and controls (95). According to Cummings, the interpretation of these findings is clouded by fundamental problems in the design and reporting of the studies. He found at least one methodologic problem in each of the 15 studies that could have substantially influenced the results. According to Mazess the results of the 15 studies, reviewed by Cummings, may have been

affected by the investigators choosing an inappropriate region to measure (R. Mazess written communication). But if Mazess is correct in suggesting that 15 studies are capable of introducing such variability, then this strongly suggests that objective interpretation of measurements obtained by different investigators might not be possible. He noted that in only one of the 15 studies did they measure the highly trabecular Wards triangle region in the proximal femur. In that study, Vose and Lockwood reported finding patients with hip fractures with substantially less bone mass at the hip than age-matched subjects (95). Investigators were not "blinded" as to the subjects' status.

Aitken has recently claimed that postural instability is the major determinant for femoral neck fracture, and that generalized osteoporosis, rather than being a prerequisite for fracture, merely determines the type of fracture sustained (102). Aitken conducted a prospective study of fractures of the femoral neck over a 12-month period in order to ascertain the relevance of generalized osteoporosis as determined by metacarpal morphometry. A total of 206 women who sustained fractures of the femoral neck after minor trauma were found to have bone mass measurements (not at the fracture site) similar to those of a control population of the same age without fractures (102). Aitken also reported that 16 percent of the women who incurred fractures had bone mass measurements similar to a group of normal premenopausal women. According to Aitken, although osteoporosis may play some part in the etiology of femoral neck fracture, it is important not to overlook the fact that over 98 percent of these fractures result from falls. He cited a study which reported that among patients aged over 50, women fell four times more often than men and that the incidence of falls rose exponentially with age up to 85 years (102). According to Aitken the results of his study and other data suggested that the absence of generalized osteoporosis was no protection against a femoral neck fracture in elderly women who fall.

To determine if osteoporosis was an important underlying cause of hip fractures

Melton and colleagues recently assessed the relationship between bone density and hip fracture incidence among women residing in Rochester, Minnesota (103). In lieu of a prospective study, the investigators obtained hip fracture incidence rates for specific femoral bone density levels by combining hip fracture incidence data covering several decades with a recent survey of BMD in the same population. BMD measurements at the cervical and intertrochanteric regions of the proximal femur were obtained using DPA. Melton found hip fractures were uncommon among women with femoral bone density greater than 1.0 g/cm^2. They also showed that hip fracture incidence rates increase as bone density decreases below the 1.0 g/cm^2 level. The greater than linear rise in hip fracture incidence observed by Melton was consistent with the reports of Bell, Carter, and Hayes that skeletal resistance to fracture varies in a nonlinear fashion with bone density (77,79).

According to Melton and associates, the cervical fracture incidence rate was 4.0 per 1,000 person-years among all women with cervical BMD less than 1.0 g/cm^2. In women with intertrochanteric BMD less than 1.0 g/cm^2 the fracture incidence was a comparable 3.7 per 1,000 person-years (103). Though the authors concluded that bone mass was an important determinant of hip fractures, they suggested that osteoporosis alone may not be sufficient to produce such fractures, since many individuals remain fracture-free even within the subgroups with the lowest bone density levels. The authors believe that osteoporosis is a necessary but not sufficient cause of age-related limb fractures. According to Melton and colleagues, studies that have matched age and sex have, in effect, matched osteoporosis as well. The failure of bone density measurements to clearly distinguish fracture patients from age-matched controls does not necessarily reflect a lack of association between osteoporosis and the risk of fracture. According to Melton, fracture risk depends on the absolute level of bone density (103). Because the

BMD measurements were obtained subsequent to the occurrence of the fractures one might regard this as fracture prevalence data in patients with fractures. It does not necessarily reflect future risk.

In an earlier work, Wicks and associates studied patients in an Australian population with fractures of the femoral neck to identify various risk factors associated with the occurrence of those fractures (104). According to Wicks, 73 percent of the 125 patients had a medical condition which could have caused a fall. The conditions included Parkinson's disease or stroke (25 percent), confusion or dementia (23 percent), cataracts or other eye disease (18 percent), and severe diabetic peripheral neuropathy (7 percent). The investigators also found that patients with fractures did not have less bone in the proximal femur than nonfractured control individuals. Examination of the femoral heads failed to reveal a single case of osteomalacia. Wicks concluded that the single most important factor leading to fracture in this population was injury caused by falls and that such injury was frequently associated with other disease processes (104). They suggested that injury causes the sudden failure of a region of the skeleton, which is fracture-prone, by virtue of mechanical factors associated with loss of bone from that site during the aging process (104).

In a recent report of risk factors for injury after a fall, Melton and Riggs reviewed the relative importance of falls versus bone loss as determinants of fracture risk (105). They pointed out that the majority of falls, even among the elderly, do not result in significant injury. They cited a study of 147 falls in a nursing home where only 1.4 percent resulted in a major injury. In another study cited by the authors of 651 falls in a home for the aged, 18 percent resulted in major injury. There were only eight cases of femoral fractures (105). They and many other investigators agree that bone loss predisposes to fractures (105). Because it has been observed that most hip fractures and other age-related fractures are associated with falls, Melton and Riggs concluded that bone loss is a necessary but not a sufficient cause of most age-related fractures (105).

They also believe that some other factor, possibly falls associated with aging are also a necessary but not sufficient cause of age-related fractures.

Physical Activity. In 1982 Krolner and associates reported using DPA bone mineral density determinations to elucidate whether the axial and the appendicular bone mass of middle-aged women with Colles' fractures differed from that of normal individuals (106). The bone mineral measurements were also used to determine whether bone mass was related to the extent of daily physical activity. BMD of the lumbar vertebrae and distal forearms were determined by DPA in 36 patients, aged 50 to 73 years with previous Colles' fracture. None of the patients had symptoms of vertebral compression fractures, and none had femoral neck fractures. The authors found that seven patients with decreased radiodensity of the vertebral bodies had normal lumbar BMD levels, and four patients with normal x-ray findings had lumbar osteopenia determined by diminished BMD. Based on a mean lumbar BMD difference of only 9 percent, the investigators suggested that skeletons of middle-aged women with Colles' fracture compared to age-matched normals have a disproportionately low trabecular bone mass (106). According to Krolner, the Colles' fracture cases represent an easily definable population who may benefit from prophylactic measures against bone loss. In 1974, after a 10-year followup of 109 women who suffered a radial fracture, Gay reported that a subsequent osteoporotic-related fracture occurred in 33 (30 percent) of the women. He came to a similar conclusion that fractures of the distal radius may be considered as a "marker" for women at risk of subsequent fractures (107). Nordin has recently reported that wrist, spine, and hip fractures are inter-related. The occurrence of one type of fracture usually indicates an increased risk of subsequent fracture at other sites. Nordin found that patients who have had a wrist fracture incur a significantly increased risk of vertebral and/or femoral neck fractures than age-matched controls (19).

According to Krolner, the DPA bone mineral density values of the lumbar vertebrae had a positive correlation to the working capacity (bicycle ergometer) of the patients

(106). Based on that relationship, the investigators suggested that the bone mass of the axial skeleton reflects the extent of the daily physical activity of the patients and that physical activity modulates the rate of bone loss from the vertebrae in middle-aged women. The findings of Krolner and associates suggested that physical exercise be considered as a prophylactic measure against vertebral bone loss in middle-aged women with Colles' fracture. An earlier epidemiological study by Chalmers and Ho also emphasized physcial activity as a possible prophylactic measure against senile osteoporosis (82). Using the incidence of hip fractures as an indication of senile osteoporosis, the investigators found the occurrence of the disease to vary greatly in different racial groups. They also found that the sex incidence also varied. According to Chalmers and Ho these differences could not be attributed to hormonal state or to the amount of dietary intake of calcium. They suggested that the differences in the incidence of hip fractures were due to the living standards of the different countries and the degree of physical activity undertaken by the different populations and sexes (82).

In 1983 Krolner and associates reported on a subsequent study that used DPA measurements of the lumbar spine in women, with a mean age of 61 years, to determine whether physical exercise could prevent involutional bone loss (108). The skeletal effects of physical training were studied in a program involving 27 of the 31 women with previous Colles' fracture of the forearm. The patients were maintained on their usual diets. Calcium supplements were not given and all medical treatment was continued. The investigators found the lumbar spine BMC of the group (N=13) exercising for 1 hour twice weekly for 8 months increased by 3.5 percent, whereas that of the control group (N=14) decreased by 2.7 percent. The authors found the difference between these changes was significant (p less than .005). However, the difference in the measurements between the beginning and the end of the study for both groups was smaller than the precision value of the DPA technique. According to the authors the results suggested that physical exercise can inhibit the involutional bone loss from the axial skeleton in

middle-aged women and lead to a net gain in axial bone mass (108). Krolner concluded, that the data support the hypothesis that involutional bone loss reflects an adaptive response to decreased physical activity, making decreased mechanical stimulation with increased age an important pathogenetic factor in osteoporosis (108).

Similarly, Rogers after reviewing studies on exercise and other factors affecting BMC concluded that the high frequency of osteoporosis in more advanced age may result largely from diminished activity during later life (75). According to Rogers, even in chickens, lack of exercise produces osteoporosis. He suggested that osteoporosis, rather than being caused physiologically by the aging process, is probably brought on by the lifestyles of older people. Also, he would include hormonal imbalance and inadequate diet as other factors which may be involved (75). In a recent cross-sectional study, Kanders and associates examined the relationship between calcium and exercise in 60 normal young women (109). They performed nutritional studies and examined the women's exercise patterns with historical data and prospectively by pedometer. The investigators found that women who had high activity patterns did not have an increased bone mass unless there was evidence that their calcium intake was above the current recommended dietary allowance (RDA). Kanders suggested that it was possible that calcium is an important cofactor for the exercise effect, and in treatment, but that by itself it is not effective.

Cummings and colleagues have reviewed the limited literature regarding the effects of exercise on the bone mass of postmenopausal women (32). They concluded that although some of the studies found a beneficial effect, the role of physical activity is inconclusive and not well studied. The inconclusive results of studies of the effect of exercise on postmenopausal women do not, however, imply that exercise is not important in preventing osteoporosis. Lifelong physical activity has been shown conclusively to increase BMC (110). Recent research in exercise and BMC has focused, however, on the decreased BMC found in young active amenorrheic women (111). In 1984, Drinkwater and

associates reported using DPA bone mass measurements of the vertebrae to determine whether the hypoestrogenic status of 14 amenorrheic athletes was associated with a decrease in regional bone mass (112). They found amenorrheic runners had 14 percent less vertebral mineral based on BMD measurements than a matched group of regularly menstruating runners. According to the investigators the BMD of the amenorrheic women, who were in their mid-20's, corresponded to that of 50-year-old women, as did their endogenous estradiol levels. Drinkwater and colleagues concluded that the results of the study did not negate the value of exercise in maintaining skeletal integrity but rather pointed out the interaction between estrogen and exercise in their effect on specific skeletal areas (112).

In a recent Australian study, Pocock and coworkers demonstrated that BMD of the femoral neck and lumbar spine in women is significantly related to variations in the level of physical fitness (113). In their study of 84 normal Caucasian women, femoral neck and lumbar spine BMD measurements by DPA were significantly correlated with fitness (predicted maximal oxygen uptake) as well as age and weight. In the 46 postmenopausal subjects, fitness was the only significant predictor of femoral neck BMD. Both weight and fitness predicted the lumbar BMD (113). According to the authors, physical fitness in this normal group accounted for 23 percent of the variation in femoral neck BMD. Pocock suggests that increased physical fitness may increase bone mass at the sites of clinically important fractures in osteoporosis and may be a useful modality in prevention of fractures at these sites (113).

Safety of DPA

Radiation exposure is always a concern with any procedure utilizing radiation sources. And while DPA is a noninvasive technique, it does involve patient exposure to radiation. Dosimetry measurements performed in the laboratory of Wahner and

colleagues at the Mayo clinic showed that a dual photon scan of the lumbar spine with a 1.5 Ci Gd-153 source gave a peak skin dose of 18 mrad with a scatter dose to the eyes of 5 mrad and to the gonads of 8 mrad (1).

Other investigators have reported similar findings. According to Mazess, the radiation dose from dual photon measurements is under 15 to 20 mrem (13). Krolner and Pors Neilsen calculated a skin dose over L3 as 10 mrad for DPA (14). They found the total dose to the ovaries to be less than 2 mrad, and the bone marrow dose less than 0.2 mrad. The radiation exposures are as low as those received from any diagnostic x-ray or nuclear medicine procedure in use today. For comparison, a typical chest x-ray exposes a patient to 20 to 40 mrad. Some investigators, such as Krolner and Pors Nielsen ensure correct positioning of the patient over the source by radiological examination and palpation (14). Besides vertebral levels, the radiograph identifies fractures and osteophytes. These routine spinal roentgenograms raise the total radiation exposure of this technique. A lumbar spine series involves an exposure of 600 mrad, with a large percentage of gonadal radiation (2).

Recently, the Department of Radiology at The Johns Hopkins University School of Medicine assessed the patient dose delivered by a dual photon absorptiometer. The system consisted of an encapsulated 1.0 Ci source of Gd-153 located 9 cm below the patient examination tabletop. Patient dose which is highest at the skin entrance surface is dependent on scan speed and line spacing. The values measured by the Department of Radiology were 5.3 mrad for the standard scan (intermediate dose) and 1.6 mrad for the survey scan (least dose). According to the investigators, these are exceptionally low-dose values that are consistent with the manufacturer's specified skin dose of less than 30 mrem. The Department of Radiology at the Johns Hopkins University School of Medicine concluded that the radiation risk associated with doses of this magnitude can be considered to be negligible (T. Beck, written communication).

DPA operators/owners need to check the current status of Nuclear Regulatory

Commission (NRC) or State licenses, which usually have to be amended before the manufacturer or other supplier will ship the Gd-153 source. Under new NRC regulations, DPA may be used by Group VI licensees whose physicians complete 8 additional hours of training (15).

DISCUSSION

The measurement of bone mass is obviously an important tool in the study of metabolic bone diseases, particularly osteoporosis. Much current interest is centered on the recent technique of DPA. This interest is a result of the applicability of the DPA technique to the spine and hip, sites of important osteoporotic fractures. Presently, DPA has utility in clinical research in studying the natural history of primary osteoporosis in large populations and in evaluating preventive and therapeutic regimens (as in the dose-response effect of estrogen). While DPA is capable of measuring bone mineral density and has advanced our knowledge of bone disease in general, its role in the management of the individual patient is uncertain.

It would be advantageous to be able to prospectively identify those women who are at risk of developing osteoporotic fractures in order to direct treatment to those at greatest risk. As a screening test for osteoporosis in perimenopausal women, this application of BMC measurements is suggested to have potential utility. Once established as a screening tool it could provide a rational basis for treating afflicted individuals or preventing osteoporosis. Although the technology to noninvasively measure bone mineral density with DPA is currently available, the ability of such measurements to identify those individuals who will subsequently have fractures has not yet been shown. There has been no prospective study demonstrating that the noninvasive measurement of bone mass can identify which patients will suffer hip, Colles', or vertebral fractures. In their 1984 review of the various noninvasive methods for bone

mineral measurements, Wahner and colleagues concluded that there was no optimal technique available for mass screening for early osteoporosis (1). The American College of Physicians' Health and Public Policy Committee recently reviewed various radiologic methods for measuring BMD, including DPA, but made no recommendation about the use of these tests in routine screening for osteoporosis (2). To predict an individual's fracture risk it would be necessary to study large population cohorts of women from various age groups and relate their specific bone measurements to prospective fracture incidence data collected over a sufficient period of time. From fracture incidence data the risk ratio could provide an estimate of risk. This type of study would enable investigators to determine whether or not it is possible to predict the risk of fracture from the initial bone density measurements. It is important to remember that a patient's bone mass measured before or at menopause may indicate whether she has low or high bone mass for her age. It will not necessarily indicate whether she will fall into the high-risk group 10 to 15 years later, when fractures begin. The contribution of bone mass at maturity versus subsequent rates of loss is still largely unknown (29). Moreover, there exists a controversy regarding the selection of a screening site. While many investigators consider BMD measurements of the actual fracture site (spine and hip) paramount, others argue that fracture risk prediction and screening can be accomplished by appendicular (trabecular) BMD measurements.

According to Grubb and coworkers, measurements of distal radius (5 mm site) bone density establish an appendicular site at which bone density losses are closely correlated with vertebral bone loss in both patient and normal populations (114). Grubb suggests that measurements at the distal radius are as good as the measurements at the spine itself for predicting vertebral fractures. This is in contrast to the reported low correlation in patient studies of bone density of radial sites to lumbar vertebral density (3,26). According to Mazess, 30 to 40 percent of patients at risk will be missed with measurements on the distal radius or the os calcis (13). In disagreement with Mazess

regarding the poor predictive values from SPA measurements, Wasnich and colleagues believe that fracture risk prediction and screening can be accomplished by appendicular (trabecular) BMD measurements (115). Recently, they found the os calcis as a suitable site for screening and the single, most clinically useful site for routine risk evaluation of perimenopausal women. However, their risk prediction data does not include any vertebral fractures incidence. Only vertebral fractures prevalence and only one hip fracture are included.

Initially, researchers used DPA bone mineral measurements in attempts to find a specific level of bone density that clearly distinguished patients with vertebral osteoporosis from those without. Those studies, including the work of Riggs and associates and Krolner and Pors Nielsen, have been largely unsuccessful (3,86). Riggs et al. found that in a comparison of spinal BMD of patients with osteoporosis with that of an age- and sex-adjusted normal range, only about 60 to 70 percent of patients with osteoporosis have values below the fifth percentile of normal (3). Krolner and Pors Nielsen found the overlap so large between patients with clinical spinal osteoporosis and age-matched normals, that the majority of patients were indistinguishable from the age-matched normals (86). Cohn and associates used a multiple logistic regression model to discriminate osteoporotic women on the basis of spinal BMD determined by DPA (116). They reported a correct classification in only 55.6 percent of the total osteoporotic subjects in the 50-59 year age group. According to Wahner, no clear bimodality exists in the distribution of bone mineral in normal persons and in patients with osteoporosis when the latter group is defined as those persons in whom spinal compression fractures are present (117). Because of the considerable overlap between the groups, and the fact that many individuals with low bone mass do not sustain fractures, Kanis concluded that bone mass may not be the major determinant of fracture and other factors such as trauma need to be considered (118).

Data from a recently published abstract suggest that bone mass is an important

determinant of vertebral fractures (119). From a population-based study of the relationship between osteoporosis and vertebral fractures Melton and colleagues at the Mayo Clinic, calculated the prevalence rate of vertebral fractures at various levels of spinal bone mineral. They found that below a bone mineral threshold of 1.40 g/cm^2 the prevalence rate increased as spinal bone mineral decreased. The possibility of a dose-response relationship would strengthen the argument for a causal relationship between bone mineral and vertebral fractures (119). While there is ample evidence to suggest that people with fractures have low bone mass,a fracture incidence data are still needed to determine the risk ratio as an estimate of future risk.

According to Cummings and colleagues, the assumption that people with the lowest bone mass are the most likely to suffer fractures appears to hold true for vertebral fractures (32). Investigators such as Riggs and colleagues who were unable to clearly distinguish patients with vertebral osteoporosis from those without, consistently found less trabecular bone, on average, in women with vertebral fractures (3). From their study of risk factors for injury after a fall, Melton and Riggs concluded that a reduction in spinal bone mass is the primary determinant of who will suffer vertebral fractures (105). According to Cummings, these findings suggest that DPA measurements of vertebral bone mineral density may be a useful way of identifying women with the greatest risk of vertebral fractures (32). The authors recommend that the use of DPA for predicting vertebral fractures should be tested in prospective studies before they are advocated for widespread use or before they are employed as a basis for recommending specific types of preventive therapy (29). While other investigators agree that, ideally, the accuracy of prediction should be demonstrated prospectively, they have attempted to find better ways of determining the magnitude of risk from cross-sectional studies in the absence of prospective studies.

It is important to consider that the ultimate benefit (fracture risk identification and guide to treatment) of early diagnosis of spinal osteoporosis by DPA measurements

will depend on the clear establishment of safe and effective treatments. While it has been shown that postmenopausal estrogen therapy currently appears to be the most effective single method for preventing bone loss and fractures in women, its use is not without risk (32). In determining whether estrogen treatment should be initiated, the physician and the menopausal patient must make a judgment based on a reasonable assessment of the relative benefits and risks to the individual patient. Varied symptoms are associated with and have been attributed to the menopause. Moreover, proposed uses for estrogen therapy in the postmenopausal period have included the prevention of coronary heart disease but this use remains controversial (48). According to Cummings and associates, et al. there is mounting evidence that estrogen therapy protects against coronary heart disease, but Haber believes the issue must currently be regarded as unsettled (32,48). They both agree that if additional evidence confirms that estrogen substantially protects against coronary heart disease, then preventing coronary heart disease would become the major indication for long-term estrogen therapy (32,48). However, it is known that postmenopausal estrogen therapy increases the risk of endometrial cancer (56). In addition to the problems of carcinoma of the uterus and possibly the breast, estrogen replacement has been associated with an increased incidence of gallbladder disease and hypertension (46). According to Johnston, problems with patient compliance and acceptance, particularly with estrogen and progesterone combinations which induce repeated episodes of bleeding related to drug withdrawal, should be noted. Cummings indicates that many of the patients on estrogen therapy discontinue the therapy within a year. There is also a high percentage of hysterectomies in this group as well, he adds (personal communication). In deciding whether to use estrogens after menopause, women and physicians may consider other factors to be at least as important as prevention of osteoporotic fractures.

The epidemiology and natural history of vertebral fractures have not been well described. Vertebral fracture may be classified either as partial vertebral deformity,

which is the partial loss of height of the anterior edge or middle section of a vertebral body, or a complete compression fracture, which is the collapse of the entire vertebral body (32). Kleerekoper and associates reviewed the various reports of vertebral fracture incidence and found that in white women over age 45 who have normal spine films, the annual incidence of complete vertebral fractures has been estimated to be about 2.3 per 1,000 women and about twice as high in women with apparently reduced spinal density (120). From a spine x-ray survey of elderly women, Marshall and associates reported that 62 percent of the 50 women between ages 65-75 showed some degree of vetebral deformity (121). However, they found that only 6 percent had collapsed vertebrae. Jensen and associates found that 5 percent of 70-year-old Danish women had complete compression fractures and an additional 18 percent had partial deformities of at least one vertebra (122). Though vertebral body deformities are prevalent in the elderly, more research is needed to determine how much pain or disability is attributable to this manifestation of osteoporosis.

Vertebral fractures occur more or less spontaneously or as the result of very minimal trauma in the course of daily living. Patients with spinal osteoporosis display considerable individual variation both in the severity of their symptoms and in subsequent fracture history. It is well recognized that many vertebral fractures are asymptomatic and are often detected only incidentally on chest or spine films long after they have occurred (120). When pain occurs, it usually subsides after several days to weeks, and by 4 to 6 weeks patients may be fully ambulatory and able to resume their normal activities. Patients with vertebral fractures are usually managed with rest and nonnarcotic analgesics. Most patients have disappearance or marked diminution of pain between episodes of vertebral body collapse. There may be intervals of several years between fractures (123). Recurrent episodes of vertebral fracture lead to progressive loss of height and increasing deformity that can cause a kyphotic "dowager's hump" posture and may lead to chronic back pain (32). A relatively small proportion of patients

develop the full crush fracture syndrome with wedging of the vertebral body and disruption of the cortex (124). While compression fractures (collapse fractures) of the vertebrae can produce severe pain, Cummings and coworkers believe that the amount of back pain and disability attributable to most vertebral fractures is unknown (32). According to Cummings there is insufficient information of the morbidity and functional consequences of vertebral fractures to justify routine screening of all postmenopausal women for that condition (99).

Recently, investigators have also applied the DPA technique of bone mineral density measurements in studies to distinguish those with a high risk of hip fracture from those with a low risk (20,101,103). Two related issues have emerged in this area of study. The first pertains to the role of osteoporosis in the occurrence of hip fractures. Investigators such as Melton and colleagues believe that age-related bone loss (osteoporosis) is a major determinant of hip fracture incidence (103). This assumption is based on the decline of BMD with age, its correlation with bone strength, and the occurrence of fractures as a function of bone strength as well as the degree of trauma. The failure of DPA bone density measurements to clearly distinguish fracture patients from age-matched controls has prompted other investigators to conclude that in addition to low bone mass, which is nearly universal among the very elderly, other factors are important in determining who will experience a hip, or Colles' fracture. (95,101,102,104). According to Bohr and Schaadt, the high incidence of hip fractures with increasing age might be explained in part by a reduction in BMC, but they concluded that other factors that reduce the strength of bone or increase the tendency to fall are also of importance (101). Wicks concluded that the single most important factor leading to fracture in the Australian population studied was injury caused by falls and that such injury was frequently associated with other disease processes. Wick and colleagues suggested that injury causes the sudden failure of a region of the skeleton which is fracture-prone by virtue of mechanical factors as well as the loss of bone from that site during the aging

process (104). Since most hip and Colles' fractures occur as the result of falls, Cummings and colleagues suggested that the tendency to fall or the inability to protect oneself from injury during a fall may be important in determining who will fracture a hip or wrist. They included microfractures and bone geometry as other characteristics of bone that may be important in determining the susceptibility of a bone to fracture (32).

Although the recent findings by Melton and associates show that it is reasonable to consider bone mass as an important determinant of the age-related hip fracture incidence, the findings did not establish the ability of DPA bone mass measurements of the hip to distinguish those with a high risk of hip fracture from those with a low risk (103). This second issue remains controversial and unproven. According to Melton, the failure of bone density measurements to clearly distinguish fracture patients from age matched controls does not necessarily reflect a lack of association between osteoporosis and the risk of fracture. If bone mass does not differ in patients with hip fractures and other elderly persons, then measurements of bone mass would be of little or no value in predicting which elderly patients are likely to incur a hip fracture. Measurements of bone mass might not be a reliable way to identify those patients at greatest risk of hip fracture. According to Melton and associates, more than 85 percent of the women 65 years and older in the general population are at risk because their BMD levels are less than 1.0 g/cm^2 (103). That being the case, treatment methods could be undertaken without the use of individual DPA bone mass measurements. It is not certain what value DPA measurements of bone will have in identifying women at greatest risk of hip or Colles' fractures. This application of the DPA method needs further clinical investigation before it is advocated for widespread use or before it is employed as a basis for recommending specific types of preventive therapy (29).

The use of DPA bone mineral measurements as an index of fracture risk is based on the assumption of an inverse correlation between the occurrence of fractures and the amount of bone mass. Although a high correlation exists between compression strength

and mineral content, other factors provide resistance to compressive stress. Physical activity may exert an effect on the trabecular structure of bone apart from its mineral composition (75). According to Bell and others, vertebral strength depends not only on BMC, but also on the trabecular structure of the vertebral body, something that cannot be measured separately by DPA (77,80).

According to Ruff and Hayes, the geometric distribution of bone tissue, together with its material properties, is critical in determining the structural strength and rigidity of the whole bone. They conclude that the most critical skeletal age changes may not be those that occur in BMC or BMD, but rather geometrical properties and material characteristics other than density. The investigators suggest that this may explain the failure of DPA measurements to clearly distinguish between high- and low-risk fracture risk individuals (80).

Although the DPA method makes it possible to obtain bone density measurements from the axial skeleton, it cannot measure purely trabecular bone. The DPA technique measures integral vertebral bone consisting of a mixture of low-turnover compact bone in the cortex, pedicles, transverse processes, and vertebral end plates. It also measures high-turnover cancellous bone in the vertebral body (55). The dense outer shell of the vertebrae (cortex) has been found to make a substantial contribution of 30 to 40 percent to the DPA measurement (7). The sensitivity of a technique that measures an integral of compact and cancellous bone may be low due to inclusion of low-turnover compact bone and extra-osseous material such as osteophytes or aortic calcification. This may place DPA measurements at a theoretical disadvantage if the measurement of purely trabecular bone provides a better method of quantifying change in a metabolic bone disease than does an integrated measure of both cortical and trabecular bone (2).

The recent findings of Hayes and Gerhart that the cortical shell contributes very little to the overall strength of the vertebral body would support the need to distinguish between cortical and trabecular components in the spine (72). Using quantitative

computed tomography, Hayes and Gerhart were able to predict the apparent density (g/cm^3) of trabecular bone in the vertebral centrum. They found that the vertebral density and cross-sectional area could be used to predict vertebral load failure (fracture) under test conditions. Hayes and Gerhart recommended clinical studies to determine whether these measurements will provide a useful tool for identifying individual patients at increased risk for spontaneous vertebral fracture (72).

A second clinical application proposed for the DPA technique has been the use of DPA measurements to monitor the effectiveness of treatment. This could apply to the treatment of individuals with established osteoporosis and also to those receiving preventive regimens. According to Lindsay, there is no current evidence that serial bone mass measurements need to be performed in patients receiving adequate estrogen, since studies indicate that more than 90 percent of these patients will be protected against bone loss (34).

Before the DPA technique is considered for general clinical practice it must be determined whether the precision of the technique is adequate to measure bone mass changes in time in one individual. The factors which determine the ability to detect changes in individual patients depend on the confidence in the measurement (confidence being inversely proportional to the coefficient of variation), the rate of change to be measured, and the duration of the study (125). The reproducibility of DPA measurements has been documented by a number of researchers, who found that the coefficient of variation was less than 5 percent (11,12,14,36,63). While some investigators have reported a 2 and 3 percent coefficient of variation for DPA, these calculations of reproducibility will tend to underestimate the reproducibility of the technique applied to individuals in nonresearch settings over prolonged periods of followup. Nevertheless, according to Kanis, a patient would have to be studied for 4 to 8 years to detect significant bone loss if the rate of bone loss was 1 percent per year and the coefficient of variation was between 2 and 5 percent (125). Age-related bone loss in the spine is about

1 percent per year in normal postmenopausal women. If the rate of bone loss was greater (2-3 percent), significant bone loss could be determined in less time, but probably not less than in 3 years which would still make the DPA technique unsuitable for serial measurements. According to Johnston, a high degree of precision in the bone mass measurement is necessary for repeated measurements of small degrees of change, and such precision is difficult to attain, even in the best controlled laboratory environment (29). According to Ott and others, until more sophisticated methods of improving the reproducibility are developed, these tests will be valuable in studying large groups of patients, but will not be as helpful in individual cases (62,91,98).

Advice and comments concerning the safety and clinical effectiveness of DPA have been sought from groups and organizations within and outside of the Federal Government. An announcement of this assessment appeared in the Federal Register notice of October 26, 1984 (126). On June 20, 1985, before the Subcommittee on Aging of the Committee on Labor and Human Resources, United States Senate, the National Institutes of Health (NIH) through the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) stated that it was a research imperative to develop methods for measuring bone density. Besides diagnosis these methods should enable early identification of bones most vulnerable to fractures and provide a measure by which to evaluate the effectiveness of new therapies (40). According to NIADDK while several noninvasive methods for measuring bone density have been developed, and DPA is among the promising techniques, presently, no existing techniques can adequately discriminate early in the disease process between normal and osteoporotic individuals (40). The NIADDK recommended long-term clinical trials of various specific patient populations in statistically significant numbers 1) to provide estimates of risk, and 2) to determine the optimal regimen to prevent bone loss and fracture.

At that same hearing on osteoporosis, the National Institute on Aging (NIA) stated that there is a need for better ways of identifying persons at high risk of fracture, since

those individuals could be expected to benefit most from treatment (37). Because it is still unclear which persons would benefit from which treatments and at what dosages and schedules, additional research and clinical trials are needed to develop the current state of knowledge regarding prevention and treatment of osteoporosis for specific individuals or groups. The American College of Obstetricians and Gynecologists (ACOG), in their statement before the Subcommittee on Aging indicated that presently, there are no tests to identfy which women are at risk for developing osteoporosis (28). The College recommended that the physician determine bone loss by aborptiometry in their diagnosis of osteoporosis. The College also recommended estrogen replacement therapy as the most effective way of slowing bone loss for those women who are at risk of developing osteoporosis (28).

Prior to the June 20, 1985 Senate Hearing on osteoporosis, the NIH Consensus Development Conference on Osteoporosis was held on April 2-4, 1984 (33). At that conference data were presented which showed that none of the noninvasive techniques for measuring bone mass were able to discriminate significantly between normal and osteoporotic individuals. None of the techniques for currently quantitating bone mass, including DPA, can definitively predict the individual at significant risk for osteopososis prior to the occurrence of fracture. The Consensus Panel concluded that osteoporosis was a major public health problem requiring additional research on the biology of human bone, defining individuals at risk, and developing safe, effective, low-cost strategies for fracture prevention. The panel recommended studies to develop accurate, safe, inexpensive methods for determining the level of risk for osteoporosis in an individual, to establish early diagnosis, and to assess the clinical course of the disease (36).

According to the Food and Drug Administration (FDA), DPAs are being marketed under Section 510(k) of the Medical Device Amendments to the Food Drug and Cosmetic Act. FDA has found DPA sufficiently similar in terms of safety and effectiveness to be considered "substantially equivalent" to single photon absorptiometers that were being

marketed prior to enactment of the Medical Device Amendments of May 28, 1976 to the Food, Drug and Cosmetics Act. Bone densitometers have been proposed for classification as Class II (Standards) devices.

Through its Clinical Efficacy Assessment Project, The American College of Physicians published a policy statement on radiologic methods to evaluate BMC in June 1984 (2). The College concluded that all methods of BMC measurement result in significant overlap between diseased and normal populations. They stated that the ultimate benefit of early diagnosis of metabolic bone disease will depend on the clear establishment of safe and effective treatments. The College believes that measurements of bone mineral content have greater utility in following the course of a disease process or assessing the effect of therapy than in establishing a diagnosis. According to the College neither CT nor DPA accurately predicts tendency to fracture and the relative value of these two techniques has not been completely established.

The Orthopaedic Research Society strongly supports continued research in the development of noninvasive techniques for understanding metabolic bone disease. The Society suggested that the research examine the precision, accuracy, sensitivity, cost, availability, and relevance to underlying metabolic bone disease of each of the techniques currently under study. The Society also suggested a workshop directed at the understanding of the surveillance of bone disease.

It is the opinion of the Society of Nuclear Medicine that bone mineral density studies should become part of the workup of patients with osteoporosis and that DPA is the technique of choice at this time. According to the Society, information on BMD provided by DPA is needed to identify patients in need of treatment for osteoporosis. They suggest it also be used to monitor patients for treatment effectiveness, to exclude patients resistant to a specific treatment regimen, and to identify the end of the effectiveness of the treatment.

A response from the American College of Nuclear Physicians concluded that

osteoporosis can be detected at its earliest stages by DPA measurements of the vertebral spine. According to the College, to postpone or prevent the problems of insidious progressive osteoporosis, early detection and screening by bone mineral analysis of the lumbar spine by DPA is critical. The College also recommends the use of repeated measurements by DPA to give information on the rate of bone loss, allow assessment of the activity of the disease, and determine the effect of the therapy.

SUMMARY

DPA is a noninvasive radiologic technique used to measure BMD in the lumbar spine and hip. The DPA technique for measuring BMD is based on measurements of radiation transmission of two separate photon energies through a medium consisting of two different materials, bone and soft tissue. The difference in photon absorption between bone and soft tissue allows for the calculation of the total bone mineral found in the scan path. With DPA the amount of bone mineral measured represents the total integrated mineral (cortical and trabecular) in the path of the beam.

The measurement of bone mass is obviously an important tool in the study of metabolic bone diseases, particularly osteoporosis. While DPA is capable of measuring bone mineral density and has advanced our knowledge of bone disease in general, its impact on the management of the individual patient is equivocal. Although the technology to noninvasively measure bone mass with DPA is currently available, the ability of such measurements to predict who is at risk of subsequently developing fractures (screening) has not yet been shown. Moreover, there exists a controversy regarding the most appropriate bone site to use for screening patients.

Studies with DPA that attempted to find a specific level of bone density that distinguished patients with vertebral osteoporosis from those without have been largely unsuccessful. Recent studies to distinguish those with a high risk of hip fracture from those with a low risk have also been unsuccessful. While recent studies indicate that a reduction in spinal bone mass is the primary determinant of who will suffer vertebral fractures, other studies have prompted investigators to conclude that in addition to low bone mass, other factors such as trauma or falls are important in determining who will experience a hip or Colles' fracture.

DPA measurements of vertebral bone mass may be a useful way of identifying women with the greatest risk of vertebral fractures, but it is not certain what value DPA

measurements of bone will have in identifying women at greatest risk of hip or Colles' fractures. These methods for predicting fractures should be tested in prospective studies before they are advocated for widespread use or before they are employed as a basis for recommending specific types of therapy.

A second clinical application proposed for the DPA technique has been the use of DPA measurements to monitor the effectiveness of treatment. A high degree of precision in the bone mass measurement is necessary for repeated measurements of small degrees of change, and such precision is difficult to attain. Presently, the suitability of the DPA technique for monitoring the effectiveness of treatment is controversial.

The ultimate benefit of early diagnosis of osteoporosis also depends on the clear establishment of safe and effective treatments. While treatment with estrogens has been found to be effective, its risks and benefits need to be assessed. Most other therapies are considered investigational.

Investigators have not distinguished between the use of DPA in clinical research and its role in day-to-day practice. DPA needs to undergo further clinical investigation before it can be recommended for general clinical use.

According to the FDA, DPAs are allowed to be marketed pursuant to Section 510(k) of the Medical Device Amendments. FDA has found DPA sufficiently similar in terms of safety and effectiveness to be considered "substantially equivalent" to single photon absorptiometers that were being marketed prior to enactment of the Medical Device Amendments of May 28, 1976 to the Food, Drug and Cosmetics Act.

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REFERENCES

1. Wahner HW, Dunn WL, Riggs BL. Assessment of bone mineral: Part 2. J Nucl Med 1984; 25(11):1241-53

2. Health and Public Policy Committee, American College of Physicians: Radiologic methods to evaluate bone mineral content. Ann Intern Med 1984;100(6):908-11.

3. Riggs BL, Wahner HW, Dunn WL, et al. Differential changes in bone mineral density of the appendicular and axial skeleton with aging. J Clin Invest 1981;67:328-35.

4. Wahner HW, Dunn WL, Riggs BL. Assessment of bone mineral: Part 1. J Nucl Med 1984;25(10):1134-41

5. Wahner HW, Dunn WL, Thorsen HC, et al. Bone mineral measurements: Review of various techniques. In Wahner HW, (ed) Nuclear Medicine: Quantitative Procedures. Boston, Little Brown and Company, 1983,pp107-32.

6. Sandler RB, Herbert DL. Quantitative bone assessments: Applications and expectations. J Am Geriatr Soc 1981;29(3):97-103.

7. Mazess RB. The noninvasive measurement of skeletal mass. In Peck WA, (ed). Bone and Mineral Research: Annual 1. Excerpta Medica, Amsterdam. 1983:223-79.

8. Mazess RB. Noninvasive measurement of bone. In Barzel US, (ed). Osteoporosis II. New York:Grune and Stratton, 1979:5-26.

9. Cameron JR, Sorenson J. Measurement of bone mineral in vivo: An improved method. Science 1963;142:230-232.

10. Lane JM, Vigtoria VJ. Current concepts review: Osteoporosis. J Bone Jnt Surg 1983;65-A(2):274-78.

11. Wilson CR, Madsen M. Dichromatic absorptiometry of vertebral bone mineral content. Invest Radiol 1977;12:180-184.

12. Dunn WL, Heinz MS, Wahner HW, Riggs BL. Measurement of bone mineral content in human vertebrae and hip by dual photon absorptiometry. Radiology 1980;136(2):485-87.

13. Mazess RB. Techniques for measuring bone loss: A comparative review. In Update on Postmenopausal Osteoporosis: Selected Proceedings from the Fourth International Congress on the Menopause, Lake Buena Vista, Florida, October 28-November 2, 1984. Biomed Info Corp 1984: 38-41.

14. Krolner B, Pors Nielsen S. Measurement of bone mineral content (BMC) of the lumbar spine, I. Theory and application of a new two-dimensional dual-photon attenuation method. Scand J Clin Lab Invest 1980; 40:653-63.

15. ECRI. Dual-photon absorptiometry for measuring bone mineral content. Issues in Health Care Technology. New technology briefs:5A3 September 1984.

16. ECRI Noninvasive bone mineral assessment. J Health Care Technol 1986; 2(3):183-200.

17. Kuntz EF. Demand for absorptiometry to expand dramatically - experts. Modern Healthcare October 11, 1985:94-95.

18. Anonymous. Proceedings of the Hahnemann University Symposium on Postmenopausal Osteoporosis: Epidemiology (second in a series). Trans Medica, Inc. N.Y. 1983.

19. Nordin BEC. Osteoporosis with particular reference to the menopause. In Avioli LV,(ed). The Osteoporotic Syndrome: Detection, Prevention, and Treatment. Grune and Stratton, N.Y. 1983:13-43.

20. Riggs BL, Wahner HW, Seeman E, et al. Changes in bone mineral density of the proximal femur and spine with aging. J Clin Invest 1982;70:716-23.

21 Anonymous. Proceedings of the Hahnemann University Symposium on Postmenopausal Osteoporosis: Etiology and Pathogenesis (third in a series). Trans Medica, Inc. N.Y. 1983.

22. Hansson T, Roos B. The influence of age, height, and weight on the bone mineral content of lumbar vertebrae. Spine 1980; 5(6):545-51.

23. Aloia JF, Vaswani A, Ellis K, et al. A model for involutional bone loss. J Lab Clin Med 1985;106(6):630-637.

24. Aurbach GD, Marx SJ, Spiegel AM. Parathyroid hormone, calcitonin, and the calciferols. In Williams RH,(ed). Textbook of Endocrinology (sixth edition). W.B. Saunders Company, Philadelphia, 1981:1006-1010.

25. Lane JM. Osteoporosis: The case for sodium fluoride and calcium. J Musculoskel Med 1984;1(8):14-24.

26 Mazess RB. On aging bone loss. Clin Orthop and Related Research 1982;165:239-52.

27 Heaney RP. Prevention of age-related osteoporosis in women. In Avioli LV,(ed). The Osteoporotic Syndrome: Detection, Prevention and Treatment. Grune and Stratton, N.Y. 1983:123-144.

28. Anonymous. Statement of the American College of Obstetricians and Gynecologists at the Osteoporosis Hearing of the Subcommittee on Aging, Senate Committee on Labor and Human Resources June 20, 1985.

29. Johnston CC. Osteoporosis-induced fractures: Criteria for risk assessment and diagnosis. In Update on Postmenopausal Osteoporosis: Selected Proceedings from the Fourth International Congress on the Menopause, Lake Buena Vista, Florida, October 28-November 2, 1984. Biomed Info Corp 1984:47-51.

30. Aloia JF, Cohn SH, Vaswani A, et al. Risk factors for postmenopausal osteoporosis. Am J Med 1985;78:95-100.

31. Johnston CC. Osteoporosis: which patients are at highest risk? J Musculo Med 1985; August 25-30.

32 Cummings SR, Kelsey JL, Nevitt C, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev 1985;7:178-208.

33. Jensen J, Christiansen C, Rodbra P. Cigarette smoking, serum estrogens, and bone loss during hormone-replacement therapy early after menopause. N Engl J Med 1985;313:973-5.

34. Lindsay R. Preventing and treating osteoporosis. In Update on Postmenopausal Osetoporosis: Selected Proceedings from the Fourth International Congress on the Menopause, Lake Buena Vista, Florida, October 28-November 2, 1984. Biomedical Information Corporation 1984:54-59.

35. Chesnut CC. Assessing risk and diagnosing established osteoporosis. In Update on Postmenopausal Osteoporosis: selected Proceedings from the Fourth International Congress on the Menopause, Lake Buena Vista, Florida, October 28-November 2, 1984. Biomed Info Corp. 1984:34-37.

36. Anonymous. Osteoporosis: Consensus Conference. JAMA 1984;252:799-802.

37. Anonymous. Statement of the National Institute of Aging at The Osteoporosis Hearing of the Subcommittee on Aging, Senate Committee on Labor and Human Resources June 20, 1985.

38. Riggs BL, Melton LJ III. Involutional osteoporosis. N Engl J Med 1986;314:1676-1686.

39. Melton LJ III, Riggs BL. Epidemiology of age-related fractures. In Avioli LV,(ed). The Osteoporotic Syndrome: Detection, Prevention, and Treatment. Grune and Stratton, N.Y. 1983:45-72.

40. Anonymous. Statement of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases at the Osteoporosis Hearing of the Subcommittee on Aging, Senate Committee on Labor and Human Resources. June 20, 1985.

41. Nordin BEC. Managing Osteoporosis: Estrogens, calcium, and other treatments. In Update on Postmenopausal Osteoporosis: Selected Proceedings from the Fourth International Congress on the Menopause, Lake Buena Vista, Florida, October 28-November 2, 1984. Biomed Info Corp 1984:74-78.

42. Johnston CC Jr., Hui SL, Longcope C. Eestrogen and calcium in the management of osteoporosis. In Dixon A. St. J, et al., (eds). Osteoporosis, A Multi-disciplinary Problem. Royal Society of Medicine International Congress and Symposium Series No. 55. Academic Press Inc. London 1983 pp 223-29.

43. Avioli LV. The management of the geriatric osteoporotic woman. In Avioli LV, ed). The Osteoporotic Syndrome: Detection, Prevention, and Treatment. Grune and Stratton, NY 1983:145-53.

44. Riggs BL. Treatment of osteoporosis with fluoride. In Dixon A. St. J., Russell RGG, Stamp TCB (ed). Osteoporosis, A Multi-disciplinary Problem. Royal Society of Medicine International Congress and Symposium Series No. 55 Academic Press Inc. London 1983.

45. Audran M, Kumar R. The physiology and pathophysiology of vitamin D. Mayo Clin Proc 1985;60:851-66.

46. Johnston CC., Jr. Studies on prevention of age-related bone loss. In Peck WA, (ed). Bone and Mineral Research: Annual 3. Elsevier, Amsterdam. 1985 pp233-57.

47. Recker RR. Prophylaxis of osteoporosis: Choosing the appropriate patient and therapy. In Update on Postmenopausal Osteoporosis: Selected Proceedings from the Fourth International Congress on the Menopause, Lake Buena Vista, Florida, October 28-November 2, 1984. Biomed Info Corp 1984:60-62.

48. Haber RJ. Should postmenopausal women be given estrogen? Medical Staff Conference, University of California, San Francisco. West J Med 1985 142:672-77.

49. Ettinger B, Genant HK, Cann CE. Menopausal bone loss can be prevented by low-dose estrogen combined with calcium supplements. In Update on Postmenooausal Osteoporosis: Selected Proceedings from the Fourth International Congress on the Menopause, Lake Buena Vista, Florida, October 28-November 2, 1984. Biomed Info Corp 1984:63-65.

50. Nordin BEC, Horsman A, Crilly RG, et al. Treatment of spinal osteoporosis in postmenopausal women. Brit Med J 1980;February 16:451-54.

51. Aloia JF. Calcitonin and osteoporosis. Geriat Med Today 1985;4(11):20-28.

52. Christiansen C. Prophylactic treatment of postmenopausal osteoporosis. In Update on Postmenopausal Osteoporosis: Selected Proceedings from The Fourth International Congress on the Menopause; Lake Bueno Vista, Florida, October 28-November 2, 1984. Biomed Info Corp 1984:66-69.

53. Riggs BL, Seeman E, Hodgson SF, et al. Effect of the fluoride/calcium regimen on vertebral fracture occurrence in postmenopausal osteoporosis. N Engl J Med 1982;306:446-50.

54. Korcok M. Add exercise to calcium in osteoporosis prevention. JAMA 1982;247:1106-12.

55. Lukert BP. Osteoporosis-A review and update. Arch Phys Med Rehabil 1982;63:480-87.

56. Buring JE, Bain CJ, Ehrmann RL. Conjugated estrogen use and risk of endometrial cancer. Am J Epidemiol 1986;124(3):434-441.

57. Shapiro S, Kelly JP, Rosenberg L, et al. Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. N Engl J Med 1985;313:969-72.

58. Ott S. Should women get screening bone mass measurements? Ann Intern Med 1986;104(16):874-876.

59. Mazess RB. Advances in single and dual-photon absorptiometry. In Christiansen C. et al., (eds). Osteoporosis: Proceedings of the Copenhagen International Symposium on Osteoporosis June 3-8, 1984, pp 57-63.

60. Genant HK. Noninvasive measurement of bone mineral is helping in early detection and monitoring of osteoporosis. Diagn Imaging 1985;Aug:52-57.

61. Genant HK, Cann CE, Boyd DP, et al. Quantitative computed tomography for vertebral mineral determination. In Frame B, Potts JT., (eds) Clinical Disorders of Bone Mineral Metabolism. Excerpta Medica, Amsterdam 1983:40-47.

62. Cohn SH. Techniques for determining the efficacy of treatment of osteoporosis. Calif Tissue Int 1982;34:433-38.

63. Roos BO, Hansson TH, Skoldborn H. Dual photon absorptiometry in lumbar vertebrae. Acta Radiol :19;111-114, 1980.

64. Peppler WW, Mazess RB, et al. Total body bone mineral and lean mass by dual-photon absorptiometry. Calcif Tissue Int 1981;33:353-59.

65. Tothill P, Smith MA, Sutton D. Dual photon absorptiometry of the spine with a low activity source of gadolinium 153. Brit J Radiol 1983;56:829-35

66. Wahner HW, Dunn WL, Offord KP, Riggs BL. Dual-photon absorptiometry: Clinical considerations In Frame B, Potts Jr. JT, (eds). Clinical disorders of bone and mineral metabolism. Excerpta Medica, International Congress Series 617;1983:34-9.

67. Schaadt O, Bohr H. Bone mineral by dual photon absorptiometry. Accuracy precision - sites of measurements in non-invasive bone measurements: methological problems. IRL Press Ltd. Oxford. Washington, D.C. 1982:59-72.

68. Krolner B, Pors Nielsen SP. Long-term reproducibility of dual photon absorptiometry of lumbar vertebrae. In Dequeker JV, Johnston CC, (eds). Non-Invasive Bone, Measurements: Methodological Problems, IRL Press, Oxford 1981:73-76.

69. LeBlanc AD, Evans HJ, Marsh C, et al. Precision of dual photon absorptiometry measurements. J Nucl Med 1986;27:1362-1365.

70. Wahner HW, Dunn WL, Mazess RB, et al. Dual-photon Gd-153 absorptiometry of bone. Radiology 1985;156:203-206.

71. Pors Nielsen S, Krolner B. Photonbeam absorptiometry. In Dixon A. St. J., et al. (eds). Osteoporosis, A Multidisciplinary Problem. Royal Society of Medicine International Congress and Symposium Series No. 55 Academic Press Inc. London 1983:105-08.

72 Hayes WC, Gerhart TN. Biomechanics of bone: Applications for assessment of bone strength. In Peck WA, (ed). Bone Mineral Research/3 Elsevier, Amsterdam 1985:259-94.

73. Martin RB, Atkinson PJ. Age and sex-related changes in the structure and strength of human femoral shaft. J Biomechan 1977;10:223-231.

74. Wall JC, Chatterji SK, Jeffery JW. Age-related changes in the density and tensile strength of human cortical bone. Calcif Tiss Intl 1979;27:105-108.

75. Rogers SL. The Aging Skeleton: Aspects of Human Bone Involution. Thomas Books, Springfield; 1982.

76. Hansson T, Roos B, Nachemson A. The bone mineral content and ultimate compressive strength of lumbar vertebrae. Spine 1980; 5((1):46-55.

77. Bell GH, Dunbar O, Beck JS, et al. Variations in strength of vertebrae with age and their relation to osteoporosis. Calc Tiss Res 1967; 1:75-86.

78. Dalen N, Hellstrom L, Jacobson B. Bone mineral content and mechanical strength of the femoral neck. Acta Orthop Scand 1976; 47:503-08.

79. Carter DR, Hayes WC. Bone compressive strength: The influence of density and strain rate. Science 1976; 194:1174-75.

80. Ruff CB, Hayes WC. Age changes in geometry and mineral content of the lower limb bones. Ann Biomed Eng 1984; 12:573-84.

81. Ruff CB, Hayes WC. Subperiosteal expansion and cortical remodeling of the human femur and tibia with aging. Science 1982; 217:945-48.

82. Chalmers J, Ho KC. Geographical variations in senile osteoporosis: The association with physical activity. J Bone and Jnt Sur 1970; 52B(4):667-75.

83. Rockoff SD, Sweet E, Bleustein J. The relative contribution of trabecular and cortical bone to the strength of human lumbar vertebrae. Calc Tiss Res 1969; 3:163-75.

84. Meunier P, Courpron P, Edouard C, et al. Physiological senile involution and pathological rarefaction of bone. Clin Endocrinol Metab 1973;2:239-56.

85. Genant HK, Cann CE, Ettinger B, et al. Quantitative computed tomography of vertebral spongiosa: A sensitive method for detecting early bone loss after oophorectomy Ann Intern Med 1982; 97:699-705.

86. Krolner B, Pors Nielsen S. Bone mineral content of the lumbar spine in normal and osteoporotic women: cross-sectional and longitudinal studies. Clinical Science 1982; 62;329-36.

87. Richelson LS, Wahner HW, Melton LJ, Riggs BL. Relative contributions of aging and estrogen deficiency to postmenopausal bone loss. N Engl J Med 1984; 311:1273-5.

88. Lindquist O, Bengtsson C, Hansson T, Roos B. Bone mineral content in relation to age and menopause in middle aged women. Scand J Clin Invest 1981;41:215-23.

89. Lindquist O, Bengtsson C, Hansson T, Jonsson R. Changes in bone mineral content of the axial skeleton in relation to aging and the menopause. Scand J Clin Lab Invest 1983;43:333-38.

90. Riggs, BL, Wahner HW, Melton LJ III, et al. Rates of bone loss in the appendicular and axial skeletons of women. J Clin Invest 1986;77:1487-1491.

91. Krolner B. Lumbar spine bone mineral content by photon beam absorptiometry. Dan Med Bull 1985;32(3):152-170.

92. Schaadt O, Bohr H. Loss of bone mineral in axial and peripheral skeleton in aging, prednisone treatment and osteoporosis. In Dequeker JV, Johnston CC, (eds). Non-Invasive Bone, Measurements: Methodological Problems, IRL Press, Oxford 1981:207-14.

93. Mazess RB. Problems in measurement of trabecular bone. In Frame B, Potts Jr. JT, (eds). Clinical Disorders of Bone and Mineral Metabolism. Excerpto Medica, International Congress Series 617; 1983:30-33.

94. Mazess RB. Noninvasive methods for quantitating trabecular bone . In Avioli LV, (ed). The Osteoporotic Syndrome: Detection, Prevention, and Treatment. Grune and Stratton, N.Y. 1983:85-114.

95. Cummings SR. Are patients with hip fractures more osteoporotic? Review of the evidence. Am J Med 1985; 78:487-94.

96. Krolner B, Berthelsen B, Nielsen SP. Assessment of vertebral osteopenia: Comparison of spinal radiography and dual-photon absorptiometry. Acta Radiologica Diagnosis 1982; 23:512-21.

97. Seeman E, Wahner HW, Offord KP, Riggs BL. Differential effects of endocrine dysfunction on the axial and the appendicular skeleton. J Clin Invest 1982; 69:1302-09

98. Ott SM, Kilcoyne RF, Chesnut CH III. Longitudinal changes in bone mass after one year as measured by different techniques in patients with osteoporosis. Calcif Tissue Int 1986;39:133-138.

99. Cummings SR, Black D. Should perimenopausal women be screened for osteoporosis? Ann Intern Med 1986;104:817-823.

100. Riggs BL, Melton LJ III. Evidence for two distinct syndromes of involutional osteoporosis. Am J Med 1983; 75 (6):899-901.

101. Bohr H, Schaadt O. Bone mineral content of femoral bone and the lumbar spine measured in women with fracture of the femoral neck by dual photon absorptiometry. Clin Orthop 1983; 179:240-45.

102. Aitken JM. Relevance of osteoporosis in women with fracture of the femoral neck. Brit Med J 1984; 288:597-601.

103. Melton LJ III, Wahner HW, Richelson LS, et al. Osteoporosis and the risk of hip fracture. Am J Epidemol 1986;124(2):254-261.

104. Wicks M, Garrett R, Vernon-Roberts B, Fazzalari N. Absence of metabolic bone disease in the proximal femur in patients with fracture of the femoral neck. J Bone Jt Surg 1982;64-B(3):319-22.

105. Melton LJ III, Riggs BL. Risk factors for injury after a fall. In Radebaugh TS, et al., (eds). Clinics In Geriatric Medicine. WB Saunders Company, Philadelphia. Volume I(3) 1985:525-39.

106. Krolner B, Tondevold E, Toft B, et al. Bone mass of the axial and appendicular skeleton in women with Colles' fracture: its relation to physical activity. Clin Physiol 1982;2:147-57.

107. Gay JD. Radial fracture as an indicator of osteoporosis: a ten year followup study. Can Med Assoc J 1974;111:156-57.

108. Krolner B, Toft B, Nielsen SP, Tondevold E. Physical exercise as prophylaxis against involutional vertebral bone loss: a controlled trial. Clin Sci 1983;64:541-46.

109. Kanders B, et al. Determinants of bone mass in young healthy women. In Christiansen C. et al., (eds). Osteoporosis: Proceedings of the Copenhagen International Symposium on Osteoporosis June 3-8, 1984.

110. Loucks AB. Exercise and osteoporosis: Findings and recommendations. In Update on Postmenopausal Osteoporosis: Selected Proceedings from the Fourth International Congress on the Menopause, Lake Buena Vista, Florida, October 28-November 2, 1984. Biomed Info Corp 1984:27-31.

111. Pels AE III. The effect of exercise on bone mineral content. In Update on Postmenopausal Osteoporosis: Selected Proceedings from the Fourth International Congress on the Menopause, Lake Buena Vista, Florida, October 28-November 2, 1984. Biomed Info Corp 1984:20-22.

112. Drinkwater BL, Nilson K, Chesnut CH III, et al. Bone mineral content of amenorrheic and eumenorrheic athletes. N Engl J Med 1984;311:277-81.

113. Pocock NA, Elsman JA, Yeates MG, et al. Physical fitness is a major determinant of femoral neck and lumbar spine bone mineral density. J Clin Invest 1986;78:618-621.

114. Grubb SA, Jacobson PC, Awlrey BJ, et al. Bone density in osteopenic women: A modified distal radius density measurement procedure to develop an "At Risk" value for use in screening women. J of Orthop Res 1984; 2:322-27.

115. Wasnich RD, Ross PDk, Heilburn LD, Vogel JM, et al. Prediction of postmenopausal fracture risk with use of bone mineral measurements. Am J Obstet Gynecol 1985;153:745-751.

116. Cohn SH, et al. Models for determining women at risk for developing osteoporosis: By total body neutron activation, photon absorptiometry of spine and radius. In Christiansen C. et al., (eds). Osteoporosis: Proceedings of the Copenhagen International Symposium on Osteoporosis June 3-8, 1984, pp 327-329.

117. Wahner HW. Assessment of metabolic bone disease: Review of new nuclear medicine procedures. Mayo Clin Proc 1985; 60:827-35.

118. Kanis JA. Treatment of osteoporotic fracture. Lancet 1984; January 7;27-33.

119. Melton LJ, et al. Bone-density-specific fracture risk: a population-based study of the relationship between osteoporosis and vertebral fracture (abstract). J Nucl Med 1985;26:p 24.

120. Kleerekoper M, Parfitt AM, Ellis BI, et al. Measurement of vertebral fracture rates in osteoporosis. In Christiansen C. et al., (eds). Osteoporosis: Proceedings of the Copenhagen International Symposium on Osteoporosis June 3-8, 1984, pp 327-329.

121. Marshall DH, et al. Fractures in elderly women: Prevalence of wrist, spine and femur fractures and their concurrence. In Christiansen C. et al., (eds). Osteoporosis: Proceedings Copenhagen International Symposium on Osteoporosis June 3-8, 1984, pp327-329.

122. Jensen GF, Christiansen C, Boesen J, et al. Epidemiology of postmenopausal spinal and long bone fractures: a unifying approach to postmenopausal osteoporosis. Clin Orthop 1982;166:75-81.

123. Krane SM, Holick MF. Metabolic bone disease. In Isselbacher KJ, et al., (eds). Harrison's Principles of Internal Medicine (ninth edition). McGraw-Hill, New York, 1980:1849-52.

124. Raisz LG. Osteoporosis. J Am Geriatr Soc 1982;30(2):127-38.

125. Kanis JA, Caulen F, Russell RGG, et al. Problems in the design of clinical trials in osteoporosis. In Dixon A. St.J., et al. (eds). Osteoporosis, a multidisciplinary problem. Royal Society of Medicine International Congress and Symposium Series No. 55 Academic Press Inc. London 1983 pp205-21.

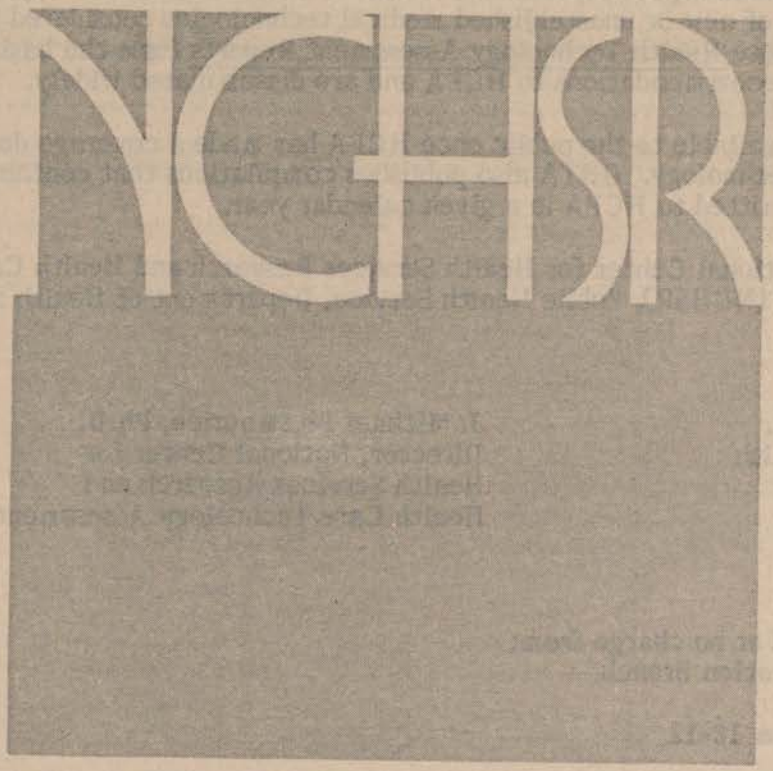
126. Federal Register 1984; 49(209):43115.

APPENDIX III - Public Health Service Assessment of Radiographic Absorptiometry for Measuring Bone Mineral Density - 1987

Health Technology Assessment Reports, 1987

Radiographic Absorptiometry for Measuring Bone Mineral Density

Number 2



NATIONAL CENTER FOR HEALTH SERVICES RESEARCH AND HEALTH CARE TECHNOLOGY ASSESSMENT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

FOREWORD

The Office of Health Technology Assessment (OHTA) evaluates the safety and effectiveness of new or unestablished medical technologies that are being considered for coverage under Medicare. These assessments are performed at the request of the Health Care Financing Administration (HCFA). They are the basis for recommendations to HCFA regarding coverage policy decisions under Medicare.

Questions about Medicare coverage for certain health care technologies are directed to HCFA by such interested parties as insurers, manufacturers, Medicare contractors, and practitioners. Those questions of a medical, scientific, or technical nature are formally referred to OHTA for assessment.

OHTA's assessment process includes a comprehensive review of the medical literature and emphasizes broad and open participation from within and outside the Federal Government. A range of expert advice is obtained by widely publicizing the plans for conducting the assessment through publication of an announcement in the Federal Register and solicitation of input from Federal agencies, medical specialty societies, insurers, and manufacturers. The involvement of these experts helps assure inclusion of the experienced and varying viewpoints needed to round out the data derived from individual scientific studies in the medical literature. After OHTA receives information from experts and the scientific literature, the results are analyzed and synthesized into an assessment report. Each report represents a detailed analysis of the safety, clinical effectiveness, and uses of new or unestablished medical technologies considered for Medicare coverage. These Health Technology Assessment Reports form the basis for the Public Health Service recommendations to HCFA and are disseminated widely.

Individual reports are available to the public once HCFA has made a coverage decision regarding the subject technology. OHTA also publishes compilations that contain all assessment reports submitted to HCFA in a given calendar year.

OHTA is part of the National Center for Health Services Research and Health Care Technology Assessment (NCHSR), Public Health Service, Department of Health and Human Services.

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ABSTRACT

Radiographic absorptiometry (RA) is a noninvasive radiologic technique involving a computer-assisted densitometric measurement of the x-ray image of bone. Mineral density analyses are based on phalangeal scans of pairs of exposed radiographs with an aluminum alloy reference wedge included in the image field. The technique can achieve a precision of 2-4 percent with a radiation dose of 10-100 mrad. While RA is capable of measuring bone mineral density and has advanced our knowledge of bone disease in general, its impact on the management of the individual patient is equivocal. Studies with RA that attempted to find a specific level of BMD that distinguished patients with osteoporosis have been largely unsuccessful. Also, the ability to predict who is at risk for subsequently developing fractures of the spine and hip has not yet been shown. Studies with RA measurements show a large scatter in the data that precludes a reliable prediction of bone mineral at one site based on measurements at another site in a particular individual. Radiographic absorptiometry needs to undergo further clinical investigation before it can be recommended for general clinical use.

PUBLIC HEALTH SERVICE REASSESSMENT OF RADIOGRAPHIC ABSORPTIOMETRY FOR MEASURING BONE MINERAL DENSITY

1987

INTRODUCTION

Radiographic absorptiometry (RA) is a noninvasive radiologic technique involving a computer-assisted densitometric measurement of the x-ray image of bone (1). Mineral density analyses are based on phalangeal scans of pairs of lightly exposed radiographs taken at different kilovoltage and exposure settings. An aluminum alloy reference wedge, which allows the computer to compensate automatically for any between-film differences in exposure, kilovoltage (kVp), filtration, film type, and film processing conditions, is included in the image field. A computer-controlled optical densitometer scans the x-ray image with a light beam. A photocell converts the light, modulated by the images, to an electrical signal that is digitized and sent to the computer for analysis and determination of bone mineral density (BMD). The system is designed to compare the findings from the patient's hand-wrist radiographs with normal values of phalangeal bone size and BMD determined from age-and sex-matched controls (2). In RA, bone mineral mass is determined and expressed as BMD (mineral concentration) by accounting for bone size (bone image area). Measurements of bone mineral by RA have been used to provide an index of skeletal status, predominantly in the assessment of renal osteodystrophy and osteoporosis.

Described in detail in 1979, RA is considered a simple, widely available, and relatively inexpensive bone mineral measurement technique (1). Similar techniques, where the optical density of bone on x-ray films is obtained under standardized conditions and used as a quantitative indicator of bone mineral content (BMC), have been used for many years (3). RA was developed in an attempt to circumvent some of the inherent limitations in the use of an x-ray image to measure BMD. Methods that measure BMD from an x-ray image have been referred to as photodensitometry, aluminum equivalency, radiographic densitometry, and radiographic absorptiometry.

According to some investigators, these methods have technical problems relating to radiographic technique and methods of film processing that limit their use (4,5). However, according to the position paper on radiologic methods to evaluate BMC from the Health and Public Policy Committee of the American College of Physicians, recent advances such as radiographic absorptiometric techniques may have reduced these problems (6).

The technique of RA utilizes image scans of the second, third, and fourth phalanges from two lightly exposed left-hand radiographs, one taken at 40-50 kVp, and the other at 50-60 kVp. An aluminum alloy reference wedge is radiographed alongside the index finger. Radiographs can be taken on any type of film without intensifying screens and with any x-ray machine. Charges for a pair of hand radiographs commonly range from $96-$160 and take from 5-10 minutes.

Using a computer-controlled scanning microdensitometer the aluminum alloy reference wedge image (on the x-ray film) is scanned. From the optical density readings (grey level) of the wedge image, the linear absorption coefficient of the wedge, and the background optical density due to film base emulsion, chemical fog and scatter are determined (2). Using the computer, these quantities are used to determine correction terms for differences between films due to different x-ray machines, kilovoltage, prefiltrations and exposure settings, film types, and film processing.

Subsequently, the scanning process is repeated for each phalangeal bone image. The scanning microdensitometer transmits a narrow beam of light through the film, traversing each bone image slice by slice. Successive parallel paths across the image of the whole phalangeal bone are scanned. Typically, 25-30 parallel scans, 1 mm apart, cover an adult middle phalangeal bone with about 200 data points per scan line (2). At the end of each scan line, the edge detection algorithm of the computer recognizes the bone edges, measures the local bone width, and generates a soft-tissue baseline. According to Colbert and Bachtell, this method computes mostly phalangeal bone mineral mass because the effects of soft tissue and matrix are substantially removed by the computation. The computer calculates the bone mineral (area density) by taking the ratio of mass to area from the densitometer's optical density readings and the bone width values (2). The mineral mass is expressed in computer units rather than in grams. The entire process is repeated for the second radiograph in order to check the results from the first analysis. The two films are taken at deliberately different kilovoltages and usually at a different milliamperage (ma) exposure in order to determine if the wedge scan and computer calculations compensate adequately for differences in radiologic technique and film processing procedures (7). The analyses are rejected if between-film disagreements greater than $\pm$ 3 percent (from their mean) can not be explained by a known system or operator error on one of the films. Otherwise, the average mineral density and bone area obtained from both radiographs are used for evaluating the patient.

The phalanges are a mixture of compact and cancellous bone, and RA does not reveal the distribution of mineral within the bone. Using RA, the bone mineral measured reflects the total integrated mineral (cortical and trabecular) in the path of the photons. Similar to the process of single photon absorptiometry (SPA), RA is limited to

measurements of appendicular bone because tissue composition surrounding the bone has to be minimal. Corrections cannot be made by this instrument for bones embedded in thick soft tissue (3).

Although the radius and other appendicular bones may be studied, the use of RA has been confined to the phalanges. Currently, the cost of analysis of a pair of films is approximately $65. A comparison of RA costs with those of other techniques for measuring bone mineral can be found in the costs section of the Office of Health Technology Assessment (OHTA) assessment for dual photon absorptiometry (DPA) (8).

Radiation exposure is always a concern with any procedure utilizing radiation sources. While RA is a noninvasive technique, it does involve patient exposure to radiation. According to the position paper on radiologic methods to evaluate BMC from the Health and Public Policy Committee of the American College of Physicians, RA involves minimal radiation exposure (up to 100 mrad), with negligible bone marrow or gonadal radiation (6). According to Chesnut, less than 10 mrem of radiation exposure are associated with the RA technique (9).

The physiologic information provided by measurements of BMC have been under extensive investigation during the past 20 years. Bone mass measurements have been a valuable research tool for clinical investigations attempting to elucidate the pathogenesis of metabolic bone diseases. Investigators have sought to determine the clinical significance of bone loss with aging and bone disease and its relationship to an increasing risk of fractures among the elderly. This growing interest in a better understanding of the nature and degree of changes in BMC with age, osteoporosis, and with metabolic bone disease in general, has prompted the development of nonivasive measurement techniques for assessing BMC (3). A variety of such techniques in addition to RA are presently available. They include: radiogrammetry, SPA, computed tomography (CT), and DPA.

Bone mineral measurements using RA have been utilized mostly in the management of patients with chronic renal failure and for osteoporosis detection in women (7). This report will reassess the effectiveness of RA bone mineral measurements on the clinical outcome of patients being evaluated and treated for osteopenic bone diseases. This reassessment seeks to ascertain the place of bone mineral evaluation by RA in the overall scheme of prevention, diagnosis and treatment. Similar reports have been published on SPA and DPA. The other noninvasive measurement techniques for BMD will be assessed in separate reports.

BACKGROUND

Osteoporosis is a major public health problem and renal osteodystrophy is a major clinical complication experienced by patients on chronic dialysis. The National Institutes of Health Consensus Development Conference on Osteoporosis held on April 2-4, 1984, reported that osteoporosis may affect between 15 and 20 million Americans (10). More than one million fractures attributable to osteoporosis occur annually in individuals over the age of 45. In women over 60, 25 percent have documented vertebral fractures by age 75. These fractures may develop during routine activities, such as bending, lifting, or raising from a chair or bed (10). While compression fractures (collapsed fractures) of the vertebrae can produce severe pain, most cases are painless. The amount of pain and disability attributable to vertebral fractures is unknown. According to the American College of Obstetricians and Gynecologists, after age 45 there is a marked increase in the incidence of distal forearm fractures (11). By age 60, there are 10 times more forearm fractures in women than in men of comparable age. These fractures limit the use of the extremity for 4-8 weeks, with long-term disability uncommon. While osteoporosis predisposes to fractures of various bones, hip fractures are the most serious in terms of disability, mortality, and aggregate cost. In the United

States, it is estimated that more than 200,000 hip fractures occur in elderly women each year with 80 percent found to be related to pre-existing osteoporosis (11). The affected population tends to be advanced in age, with the sex distribution less skewed toward females than is the case for vertebral fractures. Acute complications such as depression and mechanical failure of the surgical procedure are common (10). Most patients fail to recover normal activity. Hip fractures lead to fatalities in 12 to 20 percent of cases and precipitate long-term nursing home care for half of those who survive (12, 13). Thus hip fractures pose a significant economic as well as a medical burden.

The economic burden of all age-related fractures is great because of the large number of people involved and the expensive and protracted care that is often required. About one-fourth of all patients with limb fractures require hospitalization and the mean hospital stay increases from 13.6 days among those age 25-44, to 32.6 days among those older than age 65. Fractures of the proximal femur account for more than half of all days of hospitalization for limb fractures. In the United States, the annual cost of the acute care alone for fractures of the proximal femur has been estimated to exceed one billion dollars (14); the annual direct and indirect costs of osteoporosis, including hip fractures, are estimated to be between $3.5 billion and $6.1 billion (10,13). As a result of the considerable morbidity, mortality, and expenditures associated with this disease, there is growing interest in research regarding its prevention, diagnosis, and treatment. The pathogenesis of osteoporosis, its prevention, and its management has had extensive review. A summary of that information can be found in the osteoporosis section of the OHTA assessment on DPA (8). Additional information can also be obtained from the numerous references cited in that report.

Renal osteodystrophy is a generic term that describes a number of distinct skeletal abnormalities that are present in the majority of patients with advanced renal failure (15). Hyperparathyroidism, disorders of vitamin D metabolism, chronic metabolic acidosis, and excessive fecal losses of calcium all contribute to the occurrence of bone

diseases in uremia (16). The longer life is preserved, particularly by treatment with hemodialysis, the greater probability of developing osteodystrophy. Although clinical symptoms of bone disease are uncommon, occurring in less than 10 percent of patients with advanced renal failure, radiological and histological abnormalities are observed in about 35 and 90 percent, respectively (16).

Renal osteodystrophy is a complex disturbance of bone comprising varying degrees of osteitis fibrosa cystica, osteomalacia, osteosclerosis, and generalized osteopenia. The main components of renal osteodystrophy are osteitis fibrosa and osteomalacia. A lesser role is played by osteosclerosis and osteoporosis. The etiology is not completely understood, but impaired vitamin D metabolism, secondary hyperparathyroidism, diminished gastrointestinal absorption of calcium, and occasional aluminum toxicity all may play a role (17).

Most of the symptoms related to renal osteodystrophy appear only when renal failure is advanced (15). Manifestations of osteodystrophy include bone pain and fractures. Accompanying abnormalities include muscle weakness, soft tissue and vascular calcification and pruritus (17). Certain biochemical alterations may appear early in the course of renal insufficiency. Knowledge of the presence of these alterations may help the physician introduce treatment early in the course of renal failure and aid in the prevention of severe complications in bone and mineral metabolism (15). One of the early changes in patients with renal insufficiency is the presence of elevated levels of circulating immunoreactive parathyroid hormone (i-PTH). Parathyroid hormone increases the net release of calcium from bone into extracellular fluid. In this defense of calcium homeostasis, the hormone influences the differentiation and activities of bone cells (18).

A rise in the serum phosphate concentration is also observed when the glomerular filtration rate (GFR) below approximately 25 percent of normal. Because calcium deposition in bone is critically dependent upon the availability of phosphate, retention of

phosphate in plasma will facilitate calcium entry into the bone. This contributes to hypocalcemia and to the elevations in plasma PTH levels seen in chronic renal failure (16). Management of patients with renal osteodystrophy includes measuring and/or controlling serum levels of calcium, phosphate, and bicarbonate (15,19). These tests are presently included in the protocol of laboratory tests for the management of end-stage renal disease dialysis patients. Radioimmunoassays for monitoring the level of circulating i-PTH has also been recommended (15,18). Moreover, it has been recommended that measures for the control of the abnormal mineral metabolism of renal disease begin early in the course of the disease, when the GFR is 30-40 mL/ min (15). According to Slatopolsky and Kokko, when such treatment is instituted early in chronic renal failure, signs and symptoms of renal osteodystrophy and parathyroid gland hypertrophy may be prevented (15,19).

Conversely, Muirhead and associates have found the management of dialysis osteopenia difficult (20). They reported that measures aimed at treatment of associated metabolic bone disease, such as administration of calcium supplements, vitamin D, 1 hydroxyvitamin D_3, or parathyroidectomy, have no consistent effect on skeletal mineral content over the long term. At best, long-term treatment can be expected to slow the rate at which skeletal demineralization progresses rather than producing a sustained increase in BMC (20).

For the past 12 years, investigators have used RA to assess the BMC of the appendicular skeleton in "normal" individuals and in patients with renal osteodystrophy and osteoporosis. Few studies, however, have been conducted to investigate whether appendicular (phalangeal) bone mineral measurements could predictably separate normal women from women with vertebral compression fractures or femoral neck fractures. Investigators have also used RA measurements to identify patients ostensibly at risk for future fractures. This report examines these and other studies as well as other evidence that pertains to the safety and clinical effectiveness of this technique.

RATIONALE

The rationale for bone mineral measurements is based on the demonstration that the strength or resistance of a bone to fracture is closely related to the amount of bony tissue or the mass of the mineral present in the bone. Proponents argue that since the tensile (breaking) strength of bone is related to its mineral content, measurements of bone mineral should be a more accurate method of determining fracture risk. Proponents of RA believe that the ability to assess the direction and degree of changes in BMC in the phalanges facilitates the diagnosis and management of metabolic bone diseases, such as renal osteodystrophy and osteoporosis. Proponents also argue that these measurements could prove useful as clinical guides to therapy in assessing the therapeutic responses of patients with osteopenia. They argue that RA is low in cost and radiation exposure, uses only the x-ray equipment readily available at every hospital, and requires no special training of hospital personnel.

REVIEW OF AVAILABLE INFORMATION

Accuracy and Precision

Accuracy defines the degree to which a measurement, or an estimate based on measurements, represents the true value of the attribute that is being measured. In this case it refers to how well the measurement reflects actual mineral content. It is expressed as a coefficient of variation (or error of estimate) of the difference between actual and measured. In the determination of osteopenia, accuracy in the measurement of bone mass by RA is of great importance.

Whereas accuracy refers to the correctness with which a certain reading represents the true value, precision refers to the width of the range of indicated values. In monitoring changes in bone mass, RA bone mineral measurements have to be sufficiently precise (reproducible) to provide a correct estimate of these changes. Precision is important if the goal is to detect small changes in bone mass. The coefficient of variation (cv), expressed in percent, describes the precision or reproducibility of a given measurement.

Technical problems affecting precision and accuracy generally associated with photodensitometric methods include scattered radiation from the broad x-ray beam, a variable energy spectrum leading to uncertainties in the effective absorption coefficients of bone and soft tissue, and beam hardening of the energy spectrum in passing through soft tissue (21). Colbert and Bachtell have indicated that for small bones with thin flesh cover, such as the phalanges, the background optical density value is assumed to adequately correct for scatter if it is uniformly distributed over the bone image. In addition, the x-ray beam can be considered to have a single "effective" photon energy and there is no beam hardening (2). To minimize or prevent measurement errors that would result from different x-ray machines, kilovoltage and exposure settings, film types and film processing, Colbert and Bachtell derive correction terms from pixel data taken from a scan of the reference wedge image. According to the investigators, the wedge image is scanned to provide data for the absorption coefficient of the aluminum alloy which accounts for differences in x-ray spectrum due to tube characteristics, kilovoltage, waveform, and prefiltration. The scanning also provides the background optical density due to film base, fog, and scatter, which are a function of exposure, measured in milliampere-seconds (mA-s), and film processing procedures. Once these two values are obtained, a computer calculates the terms that automatically correct for the differences described above (2).

To minimize measurement errors due to spectrum shifts, uneven scatter distribution, incorrect film background density determinations, overexposure, underexposure, uneven film development, densitometer errors and nonlinearity, soft-tissue covering, and variations in reference wedge composition, Colbert and Bachtell recommend repeat readings averaging the results (2). They believe that system errors such as edge detection errors, computational errors, and scanner malfunction will be reduced because the mineral density data are read from three complete phalangeal bones from two separate radiographs and compared before they are averaged (2).

The instrumental accuracy of RA was studied by Colbert and co-workers in 1970 (21). Eighty-five excised bones and an aluminum reference wedge were measured under water to simulate a constant thickness of soft tissue surrounding the limb, and the mass of the ashed bone sections were compared with RA measurements. Ash weights of the bone sections ranged from approximately 0.4-2.0 g. According to the authors, the error in predicting ash weight using RA was 6 percent under these test conditions that included exposing all bones on a single radiograph under standard conditions.

To evaluate RA reliability with varying exposures, radiographs of the bone sections were made at 50 and 70 mA-s Although the measurements of the same 85 bone sections from films at 50 and 70 mA-s exposure gave a high correlation (r=0.990), the standard error of estimating indicated a prediction error of 4.4 percent (21). By averaging repeated measurements the prediction error from the different films was reduced to less than 4 percent. Colbert suggested that the use of the uniform bolus of tissue-equivalent material (water) surrounding the bone and the correction for background density of the radiograph were responsible for the increased accuracy of this technique over other photodensitometric techniques (21).

In a similar study of RA accuracy, Colbert and Barzel compared excised rat bone mineral measurements by RA with mineral content (as weight) determined gravimetrically (22). Forty-two excised rat bones and an aluminum reference wedge

were measured under several centimeters of water and the mass of the ashed bone sections were compared with RA measurements. Regression analyses showed that RA measurements again predicted ash weights within ± 6 percent.

Because the measurement error introduced by soft tissue in photodensitometric techniques has been recognized by many investigators, the procedure has usually required water immersion of the body part and wedge for correction of the effect of soft tissues (21,23). The addition of water compensates for variations in tissue thickness and provides a uniform tissue equivalent thickness (24). It also provides exposure conditions of the calibration wedge similar to those for the bone. In the 1970 and 1972 studies by Colbert and co-workers the procedure included the immersion of the body part and wedge in water.

However, in 1979, Colbert and Bachtell reported that x-rays of small bones with minimal soft-tissue cover (phalanges) do not require immersion in water (1). They found that the linear absorption coefficient of the wedge (in air) varies with photon energy in nearly the same manner as the wedge x-rayed in water and could be used in its place by applying a constant adjustment factor (1). According to Wahner and colleagues, the only photodensitometry method currently acceptable immerses the hand in water for constant soft-tissue thickness, and uses a microdensitometer and computer (3). Mazess and Cameron in agreement with Wahner and colleagues, believes that the extent of air measurement deviations (from water) depends on the effective energy of the x-ray beam (spectrum) and therefore can not be corrected by a constant multiplier (25). This issue remains controversial.

In 1983, Bachtell compared RA measured mineral weight with the ash weight of 14 phalangeal cadaver bones (26). Fourteen phalangeal cadaver bones were defleshed and radiographed in groups of two or three bones at 50 and 60 kVp. Bachtell found that the

ash weights regressed linearily against the radiological weights to give a prediction error of 3.7 percent and a correlation coefficient of 0.997. The cadaver bones and aluminum alloy reference wedge were radiographed under a thin water cover.

Results from a study of bone mass in 50 postmenopausal osteoporotic women at the University of Washington were reported by Chesnut at the National Institutes of Health (NIH) Consensus Development Conference on Osteoporosis (9). Using RA measurements of the phalanges, he found a precision of 2-3 percent. Similar levels of precision (1-4 percent) have been reported in the position paper on radiologic methods to evaluate bone mineral content from the Health and Public Policy Committee of the American College of Physicians (6). The position paper also reported 6 percent reliability (accuracy) for the RA technique.

Recent information from Bachtell and Colbert indicates that the precision of the RA technique is between 2 and 4 percent (27,28). In one cited study, BMD was determined from radiographs of a phantom hand taken over a 3-year period at eight different hospitals using nine different x-ray machines. The precision was 3.7 percent when the selection criteria of radiographs included those taken outside recommended specifications for kilovoltages and optical density (27). Allowing for changes in the system and deletion of defective radiographs and radiographs recorded outside of the specifications, the precision was improved to 2.5-3.0 percent (27,28). However, radiographs taken in violation of the recommended specifications are frequently included in BMD determinations.

In a similar study to determine the precision of the RA technique, BMD was determined from radiographs of the same left hand taken over a 10-year period at 10 different hospitals using nine different film types. The precision, depending upon the selection criteria of the radiographs, was between 2.9 and 4.1 percent (29).

Clinical Applications

In 1971, Goldsmith and co-workers used several techniques, including RA, to estimate BMC in normal and osteoporotic women (30). Using BMD values based on RA measurements of the middle phalanx of the ring and index fingers the investigators were unable to clearly separate normal women from women with moderate or severe osteoporosis.

In 1977, Colbert and colleagues reported using RA for BMD determinations in patients with chronic renal failure (31). In preliminary findings, 160 patients with chronic renal failure had average BMD values lower than reference means derived from age- and sex-matched control subjects. They believed this indicated a tendency toward osteopenia or osteodystrophy. Although the authors were reporting patient progress for less than 1 year, they recommended that patients should be followed for 3 years or more to ascertain reliable trends (31).

At the Fourth International Conference on Bone Measurement, Zanzi and co-workers presented data from a study that determined the relationship of total body calcium (TBCa), measured by total body neutron activation analysis, with BMC of the phalanges, measured by RA, and BMC of the radius measured by SPA (32). These techniques were applied to two groups of subjects: In the first group there were 16 patients (14 female, 2 male) with primary osteoporosis; and in the second group, 14 healthy male marathon runners. The investigators found a correlation between measurements of TBCa and BMC at the phalanges in the osteoporotic female population ($r=0.66$). The correlation between TBCa and BMC of the phalanges in the marathon runners was less ($r=0.57$). However, the investigators also reported that the scatter of the data could result in an error in measurement prediction of $\pm$ 7-14 percent (32).

According to Zanzi and associates, the level of correlation and standard errors of estimate attained precludes a reliable prediction of bone mineral from the phalanges to the total body in a particular individual. Used alone, TBCa data do not give a complete

separation of individual osteoporotic patients and normal subjects. Zanzi's group did suggest that RA measurements of the phalanges are adequate for use in epidemiological surveys of the bone mass of populations, or in serial evaluations of bone mass, particularly cortical bone (32).

In a continuation of the work by Colbert (31), Chester and associates studied the effectiveness of RA to assess the extent and the therapy of renal osteodystrophy (33). They compared visual review of hand radiographs with RA determinations in 179 patients with chronic renal failure. Although the investigators demonstrated some agreement between RA determinations and visual review of hand radiographs when changes were noted by the radiologist, the agreement with RA was at best moderate; they concluded that RA may be a more sensitive method of appraising renal osteodystrophy than visual reviews of hand radiographs. Chester and associates also suggested that RA determinations may indicate changes in the clinical features of renal osteodystrophy not suggested by serum calcium, phosporus, or alkaline phosphatase. This conclusion was based on a study of only eight patients with bone gain whose serum calcium, phosphorus, and alkaline phosphatase were no different (statistically) when compared to eight patients who had lost bone at an accelerated rate (33).

At the 1981 Jerusalem International Symposium on Osteoporosis, Bachtell and Colbert (34) presented data on the RA technique that updated the 1971 study by Goldsmith and associates (30). Because the mineral estimates made by the earlier RA technique did not agree with the visual osteoporosis classifications, the investigators improved the system and rescanned 49 usable radiographs from the original experiment. With the improved RA determinations, the authors found good agreement with the visual classifications. Also, the mean BMD of the normal group was significantly greater than that of the moderate plus severe osteoporotic group. However, because of the sizable overlap in BMD among the groups, bone mineral measurements of the phalanges may be unsatisfactory for evaluation of the extent of osteoporosis in an individual (34).

In a recent study, Colbert and associates used RA to determine the effect of continuous ambulatory peritoneal dialysis (CAPD) on phalangeal BMD (35). Over a 2-year period they measured and compared the BMD average rate of change of patients from one group on CAPD (N=32) and five groups on hemodialysis (N=323) with the BMD normal rate of change due to aging. Colbert and associates found that as a group, the 32 CAPD patients who had normal BMD means and distributions at baseline lost BMD, on the average, at the same rate as the controls. He also found that for four of the five patient groups on hemodialysis, BMD declined at rates significantly greater than normal. The groups were not matched for age, sex, or for any other parameters (35). After an additional year of followup, Colbert and associates confirmed their earlier findings that, on the average, the CAPD patients lose BMD at a rate not significantly different from the normal rate related to aging (36).

At the 1984 Copenhagen International Symposium on Osteoporosis, Ott and colleagues reported preliminary results of a study that compared several techniques, including RA, for the measurement of bone mass at different sites in the same group of patients (37). They sought to determine whether a measurement of bone mass at one site could predict bone mass at a second site in a population of women with postmenopausal osteoporosis. The study group consisted of 66 Caucasian women, ranging in age from 51 to 80 years, who had evidence of vertebral compression fractures. Significant but modest correlations between the various bone measurements were reported. Although measurements of TBCa and BMD at the phalanges had a significant correlation of 0.73 ($p < .001$), the investigators found that the standard error in estimating the TBCa from the other measurements was 10-15 percent. The correlation between RA measurements of the phalanges and DPA measurements of the spine was 0.56 ($p < .001$). However, the standard error in estimating the BMD at the spine from the RA phalangeal measurements was not given.

According to Ott and associates, discrepancies in measurements may be caused, in part, by the different ratios between cortical and trabecular bone at the different sites measured (37). Ott suggested that if a patient had a disproportionate loss of cortical or trabecular bone, then measurements at the spine would not correlate with those of the total body or peripheral sites.

At the same symposium, Bachtell and Colbert presented preliminary findings of a longitudinal study that used RA phalangeal mineral measurements to identify patients with a rapid loss of bone mineral (38). The investigators recorded bone mineral at 6-month intervals in 146 female subjects, mostly in their 60s, for 1 1/2-3 years. Comparing the decline of phalangeal mineral density in the 146 subjects with the average annual decline of phalangeal mineral density (1.2 percent) in a normal population of similar age, the investigators determined that 37 subjects (25 percent) of the test population had rapid loss of bone mineral (38). However, these measurements have uncertain value for predicting future rates of bone loss or assessing risk for fractures. They also ignore the fact that an accelerated bone loss has been reported in normal women following menopause.

In 1984, Bachtell noted that other investigators had observed statistically significant correlations between RA measurements of the phalanges and SPA measurements of the radius in 61 ambulatory postmenopausal osteoporotic females (39). Bachtell also compared the RA phalangeal bone mineral measurements of osteoporotic women in this group and a second similar group (N=63) with the the RA phalangeal bone mineral measurements of 377 normal females (40). An osteoporosis risk threshold was arbitrarily chosen to be one standard deviation (16 percent) below the mean mineral volume density of young normal adult women (20-50 years of age). This resulted in 80 - 90 percent of the osteoporotic females having BMD levels that fell below this value. However, values for the women in both osteoporotic groups clustered about peer norms with no significant difference between the normal mean and the subject mean. Bachtell

concluded that the osteoporosis risk threshold was an excellent discriminator of postmenopausal women who have a high risk of vertebral compression fractures. This conclusion was reached without the benefit of clinical information regarding the extent of vertebral compression fractures in the normal control group. Moreover, after age 60 almost all the women in the normal control population had values below the osteoporosis risk threshold (40).

According to Bachtell, in lieu of a prospective study to determine how well postmenopausal women who will eventually experience bone fracture can be separated from those who will not exeperience fracture, one determines how well osteoporotic women can be screened from nonosteoporotic women. In order to evaluate the screening efficacy of RA measurements, Bachtell plotted the number of true-positive results (osteoporotic women who fall below the screening threshold) from groups of confirmed osteoporotics women versus the number of false-positive results (nonosteoporotic women who fall below the threshold) from the reference females between the ages of 20 and 50. Plots of true-positive versus false-positive results are called receiver operating characteristic (ROC) curves. The higher the percentage of true-positive and the lower the percentage of false-positive results, the better the screening system (41).

Choosing a phalangeal mineral density threshold of 100 units, Bachtell was able to obtain percentages of women with true-positive results that ranged from 82-96. Using the mineral density values of the reference females between age 20 and 50, he was able to obtain a false-positive percentage of 11.5. This study demonstrated high sensitivity and high specificity of RA measurements in screening females with vertebral fracture from midlife (20-50 years) normal women. However, Bachtell showed in an earlier report that after age 60 almost all women in the normal reference population were below the osteoporosis risk threshold. This indicated that if data from a nonosteoporotic group similar in age to the osteoporotic groups were plotted, the specificity of the screening test would be low (40).

Monroe used RA measurements to screen 355 postmenopausal women for estrogen replacement therapy for prevention of postmenopausal osteoporosis (42). In 1986, he reported to the Ohio Academy of Family Physicians that a threshold of one standard deviation below the mean bone density value of normal women, 20-50 years old identified 145 (41 percent) of the women "at risk" and in need of estrogen management. Although this risk threshold is arbitrarily designated and not based on a prospective study of fracture incidence, most of the 145 women were recommended for estrogen therapy, which was accepted by 95 of them (42).

In 1986, Rosenthal and co-workers reported on a retrospective study that compared the ability of several bone measurement techniques, including quantitative computed tomography (QCT) and RA, to discriminate between patients with and without fractures (43). Selected for the study were 102 consecutive patients (74 females and 28 males) clinically suspected of having abnormally low skeletal mass; 74 of the 102 patients were age 51 or older. When patients were divided into groups with and without lumbar vertebral compression fractures, QCT provided the best separation between the two groups, ($p < .001$), with relatively little overlap. Although Rosenthal found the mean values for RA to be significantly different between the two groups, there was considerable overlap. The RA measurements of phalangeal trabecular bone were only weakly correlated with QCT measurements of spinal trabecular bone. The RA measurements of the composite mass (cortical and trabecular) of the phalanges were approximately equally correlated with the QCT measurements of spinal trabecular bone (43).

Rosenthal found that RA measurements provided the best correlation with long bone fractures (such as hip and radius); however, prediction of peripheral fractures was considered unsatisfactory by all methods. He suggested that these results may indicate that trauma is more important in the causation of extremity fractures than of vertebral compressions, a feature that cannot be predicted by any measurement (43). According to

Rosenthal, any widely useful technique for measuring bone mineral must help predict the risk of fractures in the general public. Therefore, while this retrospective study showed that QCT measurements of the spine could reasonably discriminate fracture and non-fracture patients, a prospective study is necessary to determine if those same measurements can accurately predict fracture incidence (43).

Most recently, Colbert and associates reported completing a brief study of RA-BMD measurements in 14 end-stage renal disease (ESRD) patients who subsequently underwent parathyroidectomies (44). The study was performed to determine the efficacy of RA-BMD measurements of the phalanges as an indication for surgical intervention and surgical success. This was to be determined by comparing changes in RA-BMD measurements with corresponding serum chemistries. In most instances of surgical success, as judged by serum chemistries, there was a corresponding improvement in BMD. However, Colbert acknowledged the small sample size and the need for more complete serum chemistry data and for longer observation periods in more patients. The study failed to support the conclusion of the authors that RA monitoring of phalangeal BMD is of help in deciding when to perform a parathyroidectomy on an ESRD patient. It has not been made clear by the investigators how RA bone mineral measurements would change the management based on the serum chemistries of these ESRD patients (44).

Occasionally there is a patient with severe secondary hyperparathyroidism and evidence of hypercalcemia in whom parathyroid surgery may be required to reduce excessive amounts of circulating parathyroid hormone (PTH). Close monitoring of PTH, calcium, and phosphate is essential in the management of these patients. Monitoring BMD by RA may also be of help in judging the success of the surgery and should be studied further.

DISCUSSION

The measurement of bone mass is an important tool in the study of metabolic bone diseases, particularly osteoporosis. Current interest is centered on the recent advances in bone mineral measurement techniques including RA. This interest in RA is based on the belief that bone mineral measurements of the phalanges facilitates the diagnosis and management of metabolic bone diseases, such as renal osteodystrophy and osteoporosis. Presently, RA has utility in clinical research in studying the natural history of primary osteoporosis and renal osteodystrophy in large populations and in studies evaluating preventive and therapeutic regimens. However, while RA is capable of measuring bone mineral and has advanced our knowledge of bone disease in general, its role in the management of the individual patient is uncertain.

It would be advantageous to be able to prospectively identify those women who are at risk for developing osteoporotic fractures, in order to direct treatment to those at greatest risk. As a screening test for osteoporosis in perimenopausal women, this application of RA bone mineral measurements is suggested to have potential utility. Once established as a screening tool it could be used in the strategy for treating afflicted individuals or preventing osteoporosis. Although the technology to noninvasively measure bone mineral with RA is currently available, the ability of such measurements to identify those individuals who will subsequently experience bone fracture has not yet been shown.

Presently, there has been no prospective study demonstrating that the noninvasive measurement of bone mass by RA can identify patients who will suffer fractures. In their 1984 review of the various noninvasive methods for bone mineral measurements, Wahner and colleagues concluded that there was no optimal technique available for mass screening for early osteoporosis (45). The American College of Physicians' Health and Public Policy Committee recently reviewed various radiologic methods for measuring BMD, including RA, but made no recommendation about the use of these tests in routine

screening for osteoporosis (6). In order to predict a female individuals' fracture risk, it would be necessary to study large population cohorts of women from various age groups and relate their specific bone measurements to prospective fracture incidence data collected over a sufficient period of time. Using fracture incidence data, the risk ratio would provide an estimate of risk. This type of study would enable investigators to determine whether it was possible to predict the risk of fracture from the initial bone density measurements. A patient's bone mass measured before or at menopause may indicate whether she has low or high bone mass for her age. It will not necessarily indicate whether she will fall into the high-risk group 10-15 years later, when most fractures occur. The contribution of bone mass at maturity versus subsequent rates of loss is still largely unknown. Moreover, there exists a controversy regarding the selection of a screening site. While many investigators consider BMD measurements of the actual fracture site (spine and hip) paramount, others argue that fracture risk prediction and screening can be accomplished by appendicular BMD measurements. According to Riggs and Melton, appendicular measurements would be of little value for predicting the risk of fracture in the spine or hip (13).

Initially, investigators used RA bone mineral measurements in attempts to find a specific level of bone density that clearly distinguished patients with vertebral osteoporosis. Those studies, including the work of Bachtell and Colbert and more recently Rosenthal and co-workers, have been largely unsuccessful in determining such a level (34,43). When patients were divided into groups with and without lumbar vertebral compression fractures, Rosenthal found that the mean values for RA differed significantly between the two groups, but there was considerable overlap (43). Other investigtors, such as Riggs and colleagues, who also were unable to clearly distinguish patients with vertebral osteoporosis, consistently found less trabecular bone, on average, in women with vertebral fractures (46). From their study of risk factors for injury after a fall, Melton and Riggs concluded that a reduction in spinal bone mass is the primary

determinant of who will suffer vertebral fractures (47). According to Cummings and associates, measurement of vertebral BMD may be a useful way of identifying women at greatest risk for vertebral fractures (48).

With regard to peripheral fractures (hip and radius), Rosenthal considered separation of patients with peripheral fractures unsatisfactory by all methods of measuring bone mineral, including RA. He suggested that trauma may be more important in causation of extremity fractures than of vertebral compressions, a feature that can not be predicted by any measurement (43). The failure of other bone density measurement techniques to clearly distinguish fracture patients from age-matched controls has prompted other investigators to concur that in addition to low bone mass, which is nearly universal among the very elderly, other factors are important in predicting who will experience a hip, or Colles' fracture.

Other studies of RA investigated the correlation between bone density measurements of the phalanges and TBCa measured by total body neutron activation analysis (32,37). The studies by Zanzi and co-workers and Ott and colleagues indicated that a correlation between measurements at two sites (phalanges and total body) does not necessarily mean that one measurement may accurately predict the other (32,37). Even significantly correlated measurements with a large standard error (scatter) precludes a reliable prediction of bone mineral at one site based on measurements at another site in a particular individual.

In two studies, RA measurements of phanageal BMD were, at best, only moderately correlated with spinal BMD measurements (37,43). According to Ott and associates, if a patient has a disproportionate loss of cortical or trabecular bone, measurements at the spine would not correlate with those of the total body or peripheral sites.

In 1984, when Bachtell compared the RA phalangeal bone mineral measurements of two groups of osteoporotic women with a large group of normal females, he found that the measurements in both osteoporotic groups clustered about peer norms with no

significant difference between the normal mean and the subject mean (40). However, by arbitrarily choosing a phalangeal mineral density of 100 units and comparing the BMD values of these osteoporotic postmenopausal women with the BMD values of normal females 20-50 years of age, he was able to distinguish patients with osteoporosis. After age 60 almost all the women in the normal control population were below the osteoporosis risk threshold (40).

If phalangeal bone mass in the elderly does not differ in patients with and without fractures, these measurements would be of little or no value in predicting which elderly patients are likely to incur a fracture. Measurements of phalangeal bone mass may not be a reliable way to identify those at greatest risk for fracture. According to Bachtell, almost all the women 60 years and older in the normal reference population are at risk because their BMD values are below the phalangeal mineral density threshold of 100 units (40). That being the case, treatment methods could be undertaken without the use of individual RA bone mineral measurements. It is not certain what value RA measurements of phalangeal bone will have in identifying women at greatest risk for fracture. This application of the RA method needs further clinical investigation before it is advocated for widespread use or before it is employed as a basis for recommending specific types of preventive therapy.

Another clinical application proposed for the RA technique has been the use of RA measurements to monitor the rates of bone loss and the effectiveness of treatment. This could apply to the treatment of individuals with established osteoporosis and also to those receiving preventive regimens. Because rates of bone loss are relatively small compared with the reproducibility of the measurement, current methods for measuring bone mass, including RA, may not be sufficiently precise for clinical decisions in an individual (49,50). As stated earlier RA is reported to have a precision of 2-4 percent, and the average rate of appendicular bone loss in women is 1 percent per year in the decade after, and less before, natural menopause. According to Cummings and Black, for

women, a measurement of the rate of bone loss based on two measurements of bone mass over a period of time leaves considerable uncertainty about the rate of loss. A bone loss of 3 percent measured by a technique with a 2-percent reproducibility (RA) leaves a considerable uncertainty about the actual rate of loss (the 90 percent confidence interval for that change in bone mass varies from a 1.7 percent gain to a 7.7 percent loss) (49). Unless multiple measurements are made, a woman must lose a substantial amount of bone during the time between measurements before a physician can conclude that she is losing bone more rapidly than normal (49). However, even these additional measurements have uncertain value for predicting future rates of bone loss or assessing risk for fractures and would substantially increase the expense of management. Riggs and Melton believe that measurements every 6 months over 2-3 years may be required to estimate individual rates of bone loss (13). According to Ott, until such time as more sophisticated methods of improving the reproducibility are developed, techniques for measuring bone mineral, such as RA will be valuable in studying large groups of patients, but will not be helpful in individuals (50).

Still uncertain, however, is the suitability of the phalangeal bone site as the appropriate location to determine rates of bone loss or the effectiveness of treatment. Even if the RA technique is shown to be adequate for determining rates of bone loss or gain by sequential measurements, there would be uncertainty as to whether the results would reliably reflect bone loss or gain in the spine or hip. Moreover, according to Lindsay and mentioned at the recent NIH Workshop on Osteoporosis, there is no current evidence that serial bone mass measurments need to be performed in patients receiving adequate estrogen therapy, since studies indicate that more than 90 percent of these patients will be protected against bone loss (51).

Some investigators have reported using RA measurements of phalangeal BMD to assess the extent and the therapy of renal osteodystrophy (31,33). Colbert and associates have investigated the efficacy of RA-BMD measurements of the phalanges as an

indication for parathyroid surgical intervention and success (44). Because biochemical alterations may appear early in the course of renal insufficiency, the prevention and management of renal osteodystrophy includes the control and monitoring of serum calcium and phosphate concentrations (15).

Secondary hyperparathyroidism with renal osteodystrophy is a frequent if not universal complication of chronic hemodialysis (52). Phosphate retention, developing early in renal compromise, contributes to most of the components of renal osteodystrophy (17). The initial stimulus of secondary hyperparathyroidism is believed to be a chronic reduction of ionized calcium in the extracellular fluid due to renal retention of phosphate (53). Because calcium deposition in bone is critically dependent upon the availability of phosphate, retention of phosphate in plasma facilitates calcium entry into bone and contributes to the hypocalcemia observed in chronic renal failure.

Secondary hyperparathyroidism is a state of compensatory hypersecretion of PTH and may occur where there is a tendency toward hypocalcemia. Excessive levels of PTH accounts for many of the bone changes of renal osteodystrophy, including osteitis fibrosa and osteosclerosis (54). Importantly, one of the early changes in patients with renal insufficiency is the presence of elevated levels of circulating i-PTH. Knowledge of the presence of these and other biochemical alterations should help the clinician to introduce treatment early in cases of renal failure and aid in the prevention of severe complications in bone and mineral metabolism (15). According to Clark, maintaining relatively normal serum concentrations of calcium and phosphorus during hemodialysis has dramatically decreased incidence of bone disease (52). Drach recommends obtaining a fasting serum calcium level with a simultaneous measurement of serum PTH (55).

A review of the literature indicates that the information regarding the levels of calcium, phosphate, i-PTH, and other chemical entities obtained from clinical chemistry testing, is sufficient for the management of renal osteodystrophy. The need or

appropriateness for RA-BMD measurements of the phalanges in the management of renal osteodystrophy has not been established in the studies presented.

Advice and comments concerning the safety and clinical effectiveness of RA has been sought from groups and organizations within and outside of the Federal government. An announcement of this assessment appeared in the Federal Register notice of October 26, 1984 (56). On June 20, 1985, in testimony before the Subcommittee on Aging of the Committee on Labor and Human Resources, United States Senate, representatives of NIH, through the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), stated that it was a research imperative to develop better methods for measuring bone density (57). In addition to diagnosis, these methods should enable early identification of bones most vulnerable to fracture and provide a measure by which to evaluate the effectiveness of new therapies. According to NIADDK, while several noninvasive methods for measuring bone density have been developed, at present no existing techniques can adequately discriminate, early in the disease process, between normal and osteoporotic individuals (57). The NIADDK recommended long-term clinical trials of various specific patient populations, in numbers large enough to provide valid and reliable estimates of risk, and to determine the optimal regimens to prevent bone loss and fracture.

At that same hearing on osteoporosis, the National Institute on Aging (NIA) stated that there is a need for better ways of identifying persons at high risk for fracture, since those individuals could be expected to benefit most from treatment (12). Because it is still unclear which persons would benefit from which treatment, and at what dosages and schedules, additional research and clinical trials are needed to develop the current state of knowledge regarding prevention and treatment of osteoporosis for specific individuals or groups. The American College of Obstetricians and Gynecologists, in their statement before the Subcommittee on Aging, indicated that presently there are no tests to identify

which women are at risk for developing osteoporosis (11). The College recommended, however, that the physician determine bone loss by absorptiometry in their diagnosis of osteoporosis.

The NIH Consensus Development Conference on Osteoporosis was held on April 2-4, 1984 (10), approximately 14 months prior to the Senate Hearing on Osteoporosis. At that conference, data were presented that showed that none of the noninvasive techniques for measuring bone mass were able to significantly discriminate between normal and osteoporotic individuals. None of the techniques for currently quantitating bone mass can definitely predict the individual at significant risk for fracture. The Consensus Panel concluded that osteoporosis was a major public health problem requiring additional research on the biology of human bone, defining individuals at risk, and developing safe, effective, low-cost strategies for fracture prevention (10). The panel recommended studies to develop accurate, safe, inexpensive methods for determining the level of risk for osteoporosis in an individual, to establish early diagnosis, and to assess the clinical causes of the disease (10).

In February of 1987, as a followup to the Consensus Development Conference, NIH sponsored a scientific workshop on research directions in osteoporosis (58). Quantitative computed tomography, SPA, and DPA were discussed and listed as methods that offered a dramatic improvement over previously available methods of determining BMD. The group reported that measurements of bone mass or change in bone mass in peripheral sites do not accurately reflect bone mass or change at axial sites (spine or hip), which are areas of greater interest. Consequently, measurements at any one site do not allow prediction of mass or change in mass at another site in an individual (58).

According to the Food and Drug Administration (FDA), the laboratory presently using the RA technique to read radiographs is providing a service, and, as such, is <u>not</u> actively regulated by the FDA.

In June 1984, through its Clinical Efficacy Assessment Project, The American College of Physicians published a policy statement on radiologic methods to evaluate BMC (6). The College concluded that all methods of BMC measurements result in significant overlap between diseased and normal populations. They stated that the ultimate benefit of early diagnosis of metabolic bone disease will depend on the clear establishment of safe and effective treatment. The College believes that measurements of BMC have greater utility in following the course of disease process or assessing the effect of therapy than in establishing a diagnosis. According to the College, none of the available techniques, including RA, accurately predict the tendency to fracture (6).

The Orthopedic Research Society strongly supports continued research in the development of noninvasive techniques for understanding metabolic bone disease. The Society suggested that research examine the precision, accuracy, sensitivitiy, cost, availability, and relevance to underlying metabolic disease of each of the techniques currently under study. The society also suggested holding a workshop directed at the understanding of the surveillance of bone disease.

It is the opinion of the Society of Nuclear Medicine that bone mineral density studies should become part of the workup of patients with osteoporosis and that DPA is the technique of choice at this time. According to the Society, other methods performed on appendicular bone are of little value in patients with osteoporosis. However, they may have some application in patients with renal bone disease.

A response from the American College of Nuclear Physicians stated that osteoporosis can be detected at its earliest stages by DPA measurements of the vertebral spine. According to the College, in order postpone or prevent the problems of insidious progressive osteoporosis, early detection and screening by bone mineral analysis of the

lumbar spine by DPA is critical. The College finds DPA of the spine far superior to appendicular measurements in detecting most cases of early osteoporosis. They suggest, however, that in older patients with significant degenerative spine disease, appendicular measurements may be helpful in management on an individual basis.

SUMMARY

Radiographic absortiometry is a noninvasive radiologic technique involving a computer-assisted densitometric measurement of the x-ray image of bone. Mineral density analyses are based on phalangeal scans of pairs of lightly exposed radiographs with an aluminum alloy reference wedge included in the image field. After a computer-controlled optical densitometer scans the x-ray image with a light beam, the system is designed to compare the findings with normal values of phalangeal bone size and BMD determined from age- and sex-matched controls. In RA, bone mineral mass is determined and expressed as BMD (mineral concentration) by accounting for bone size (bone image area). Using currently available equipment, the technique can achieve a precision of 2-4 percent with a radiation dose of 10-100 mrad.

The measurement of bone mass is an important tool in the study of metabolic bone diseases, such as osteoporosis and renal osteodystrophy. While RA is capable of measuring BMD and has advanced our knowledge of bone disease in general, its impact on the management of the individual patient is equivocal. Although the technology to measure bone mass noninvasively with RA is currently available, the ability of such measurements at the phalanges to predict individuals at risk for subsequently developing fractures of the spine and hip (screening) has not yet been shown.

Studies with RA that attempted to find a specific level of bone density that distinguished patients with vertebral osteoporosis have been largely unsuccessful. Other studies with RA measurements have reported statistically significant correlations

between bone density of the phalanges and that of total body calcium. However, a large scatter in the data precludes a reliable prediction of bone mineral from one site based on measurements at another site in an individual.

Other clinical applications proposed for the RA technique are to monitor rates of bone loss and to determine the effectiveness of treatment. A high degree of precision in the bone mass measurement is necessary for repeated measurements of small degrees of change, and such precision is difficult to attain. Presently, the suitability of the phalangeal site for monitoring changes in bone loss is questionable.

Investigators have not established the need or appropriateness of RA measurements in the management of renal osteodystrophy for ESRD patients. Radiographic absorptiometry needs to undergo further clinical investigation before it can be recommended for general clinical use.

With regard to its regulatory status, the Food and Drug Administration stated that the laboratory presently using the RA technique to read radiographs is providing a service, and as such is not actively regulated by the FDA.

Prepared by: Martin Erlichman, M.S.

REFERENCES

1. Colbert C, Bachtell RS, Bailey J. Radiographic absorptiometry: System for following mineral changes in patients with bone disease. Presented at the XIIth International Conference on Medical and Biological Engineering and Vth International Conference on Medical Physics, Jerusalem, Israel, August 19-24, 1979.

2. Colbert C, Bachtell RS. Radiographic Absorptiometry, in Cohn SH, (ed): Non-Invasive Measurement of Bone Mass and Their Clinical Application. Boca Raton, FL. CRC Press, 1981

3. Wahner HW, Dunn WL, Riggs BL. Assessment of bone mineral, Part 1. J Nucl Med 1984;25:1134-1141.

4. Mazess RB. Noninvasive measurement of bone, in Barzel US, (ed): Osteoporosis II. New York:Grune and Stratton, 1979, pp 5-26.

5. Wahner HW, Dunn WL, Thorsen HC, et al. Bone mineral measurements: Review of of various techniques, in: Wahner HW (ed): Nuclear Medicine: Quantitative Procedures. Boston, Little Brown and Company, 1983, pp 107-32.

6. Health and Public Policy Committee, American College of Physicians. Radiologic method to evaluate bone mineral content. Ann Intern Med 1984;100(6):908-11.

7. Colbert C, Bachtell RS, Baldwin CJ, Jerison AD. Minimizing health care costs: Bone mineral change determination in renal failure and osteoporosis from x-rays of the hand. Proceedings of the Sixth Annual Symposium on Computer Applications in Medical Care, Oct-Nov 1982.

8. National Center for Health Services Research and Health Care Technology Assessment. Public Health Service. Health Technology Assessment Report: Dual Photon Absorptiometry for Measuring Bone Mineral Density, 1986 (6).

9. Chestnut CH. Noninvasive techniques in the diagnosis of osteoporosis. Presented at the National Institutes of Health Consensus Development Conference on Osteoporosis, April 2-4, 1984

10. Osteoporosis. JAMA 1984;252(6):799-802.

11. Statement of the American College of Obstetricians and Gynecologists Osteoporosis Hearing of the Subcommittee on Aging, Senate Committee on Labor and Human Resources, June 20, 1985.

12. Statement of the National Institutes of Aging at the Osteoporosis Hearing of the Subcommittee on Aging, Senate Committee on Labor and Human Resources, June 20, 1985.

13. Riggs LB, Melton LJ. Involutional osteoporosis. N Engl J Med 1986;314: 1676-1686.

14. Melton LJ, Riggs BL. Epidemiology of age-related fractures, in Avioli LV, (ed): The Osteoporotic Syndrome: Detection, Prevention and Treatment. New York Grune and Stratton, 1983, pp 45-72.

15. Slatopolsky E. Renal osteodystrophy, in Wyngaarden JB, Smith Jr. LH, (eds): Cecil Textbook of Medicine. Philadelphia: WB Saunders Company, 1985, pp. 1453-56.

16. Brenner BM, Lazarus JM. Chronic renal failure: Pathophysiologic and clinical considerations, in Petersdorf RG, Adams RD, Brauwald E, et al, (eds): Harrison's Principles of Internal Medicine, 10th ed. New York: McGraw-Hill Book Company, 1983, pp 1616-17.

17. Aurbach GD, Marx SJ, Spiegel AM. Metabolic bone disease in Wilson JD, Foster DW, (eds): Williams Textbook of Endocrinology, 7th ed. Philadelphia: WB Saunders Company, 1985, p 17.

18. Arnaud CD. The parathyroid glands, hypercalcemia, and hypocalcemia, in Wyngaarden JB, Smith LH Jr. (eds): Cecil Textbook of Medicine. Philadelphia: WB Saunders Company, 1985, pp 1434-35.

19. Kokko J. Chronic renal failure, in Wyngaarden JB, Smith LH Jr, (eds): Cecil Textbook of Medicine. Philadelphia: WB Saunders Company, 1985, p 557.

20. Muirhead N, Kerr DNS, Ward MK, Aird EGA. Osteoporosis in renal diseases and dialysis, in Dixon RGG, Russell and Stamp TCB (eds): Osteoporosis, A Multidisciplinary Problem. Royal Society of Medicine International Congress and Symposium Series No. 55 London: Academic Press and the Royal Society of Medicine, 1983, pp 173-77.

21. Colbert C, Mazess RB, Schmidt PB. Bone mineral determination in vitro by radiographic photodensitometry and direct photon absorptiometry. Invest Radiol 1970;5:336-40.

22. Colbert C, Barzel US. Radiographic determination of rat bone mineral loss in dietary-induced osteoporosis. Invest Radiol 1972;7:339-40.

23. Meema HE, Harris CK, Porrett RE. A method for determination of bone-salt content of cortical bone. Radiology 1964;82(6):986-97.

24. Vogel JM, Anderson JT. Rectilinear transmission scanning of irregular bones for quantification of mineral content. J Nucl Med 1972;13(1):13-18.

25. Written Communication, Mazess R, Cameron J. March 15, 1985.

26. Written Communication, Bachtell R. March 16, 1983.

27. Written Communication, Bachtell R, Colbert C. September 30, 1983.

28. Written Communication, Bachtell R, Colbert C. October 16, 1986.

29. Written Communication, Bachtell R, Colbert C. October 1986.

30. Goldsmith NF, Johnston JO, Ury H, et al. Bone-mineral estimation in normal and osteoporotic women. J Bone and Joint Surg 1971;53-A(1):83-100.

31. Colbert C, Bachtell RS, Sharp R, et al. Bone mineral density in chronic renal failure. Dialyses Transplant 1977; April:77-83.

32. Zanzi I, Colbert C, Bachtell R, et al. Comparison of total-body calcium with radiographic and photon absorptiometric measurements of appendicular bone mineral content, in Mazess RB (ed): Proceedings Fourth International Conference on Bone Measurement, Ontario Canada, June 1-3, 1978. NIH Publication No 80-1983, May 1980, pp 393-400.

33. Chester AC, Diamond LH, Smith RE, et al. Photodensitometry in chronic hemodialysis, in Mazess RB (ed): Proceedings Fourth International Conference on Bone Measurement, Ontario Canada June 1-3, 1978. NIH Publication No.80-1938 May 1980, pp 441-46.

34. Bachtell RS, Colbert C. Mineral computed from phalangeal x-rays compared with osteoporosis index assessed from spinal x-rays, in: Menczel J, Robin GC, Steinberg R (eds): Osteoporosis: The Proceeding of an International Symposium, Jerusalem Osteoporosis Center, June 1981. Chichester, England: John Wiley and Sons, 1981, pp 98-108.

35. Colbert C, Jerison A, Bachtell RS, The effect of CAPD on phalangeal bone mineral density. Peritoneal Dialysis Bulletin-Supplement, Jul-Sept 1984; 4(3):148-51.

36. Colbert C, Jerison A, Bachtell RS. The effect of CAPD on phalangeal bone mineral density: Part II. Peritoneal Dialysis Bulletin, 1985.

37 Ott SM, Chesnut CH, Hanson JA, et al. Comparison of bone mass measurements using different diagnostic techniques in patients with postmenopausal osteoporosis, in Christiansen C, Arnaud CD, Nordin BEC, et al (eds): Osteoporosis: Proceedings of the Copenhagen International Symposium on Osteoporosis, June, 3-8, 1984, pp 93-6.

38. Bachtell RS, Colbert C. Identification of fast losers from longitudinal phalangeal mineral measurements in Christiansen C, Arnaud CD, Nordin BEC, et al. (eds): Osteoporosis: Proceedings of the Copenhagen International Symposium on Osteoporosis, June 3-8, 1984, pp 345-47.

39. Written Communication, Bachtell R. March 14, 1984.

40. Written Communication, Bachtell R. April 19, 1984.

41. Written Communication, Bachtell R. December 4, 1985.

42. Monroe EP. Osteoporosis screening by radiographic absorptiometry. Presented at the Ohio Academy of Family Physicians Research Day, Columbus Ohio, February 1986.

43. Rosenthal DI, Gregg GA, Schoenfeld D, et al. A comparison of quantitative computed tomography to four techniques of upper extremity bone mass measurement, in press.

44. Colbert C, Twardowski ZJ, Van Stone JC, Nolph KD, et al. The influence of parathyroidectomy and bone mineral density and serum chemistries in dialysis patients, unpublished data.

45. Wahner HW, Dunn B, Riggs L. Assessment of bone mineral: Part 2. J Nucl Med 1984;25(11):1241-1253.

46. Riggs BL, Wahner HW, Dunn WL, et al. Differential changes in bone mineral density of the appendicular and axial skeleton with aging. J Clin Invest 1981;67:28-35.

47. Melton LJ III, Riggs BL. Risk factors for injury after a fall, in: Radebaugh TS, et al, (eds): Clinics In Geriatric Medicine Vol 1, No. 3. Philadelphia: WB Saunders Company, 1985, pp 525-539.

48. Cummings SR, Kelsey JL, Nevitt C, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev 1985;7:178-208.

49. Cummings SR, Black D. Should perimenopausal women be screened for osteoporosis? Ann Intern Med 1986;104:817-823.

50. Ott S. Should women get screening bone mass measurements? Ann Intern Med 1986;104(6):874-76.

51. Lindsay R. Preventing and treating osteoporosis in Update on Post-menopausal Osteoporosis: Selected Proceedings from the Fourth International Congress on the Menopause, Lake Buena Vista, Florida, October 28-November 2, 1984. Biomedical Information Corporation, 1984, pp 54-59.

52. Clark OH. Thyroid and parathyroid,in Dunphy JE, Way LW (eds): Current Surgical Diagnosis and Treatment. 5th ed. Los Altos, Calif: Large Medical Publications, Dunphy JE, Way LW (eds): 1981, p 247.

53. Aurbach GD, Marx SJ, Spiegel AM. Parathyroid hormone, calcitonin, and the calciferols in Wilson JD, Foster DW, (eds): Williams' Textbook of Endocrinology, 7th ed: Philadelphia: WB Saunders Company, 1985, p. 1187.

54. Brenner BM, Hostetter TH. Disturbances of renal functions in Petersdorf RG, Adams RD, Brauwald E, et al, (eds): Harrison's Principles of Internal Medicine, 10th ed. New York: McGraw-Hill Company, 1983, p 1604.

55. Drach GW. Urinary lithiasis in Campbell's Urology 5th ed. Philadelpia: WB Saunders Company, 1986, p 1148.

56. Federal Register 1984;49(209):43115.

57. Statement of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases. Osteoporosis Hearing of the Subcommittee on Aging, Senate Committee on Labor and Human Resources June 20, 1985.

58. Statement of the NIH Scientific Workshop Research Direction in Osteoporosis. February 9-11, 1987.

[FR Doc. 88-20408 Filed 9-7-88; 8:45 am]
BILLING CODE 4120-01-C

federal register

Thursday
September 8, 1988

Part V

Environmental Protection Agency

40 CFR Part 167

Registration of Pesticide and Active Ingredient-Producing Establishments, Submission of Pesticide Reports; Final Rule

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 167

[OPP-70000A; FRL-3363-9]

Registration of Pesticide and Active Ingredient-Producting Establishments, Submission of Pesticide Reports

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This rule requires that producers of pesticide active ingredients register their establishments and submit reports to EPA. The Agency is taking this action in response to a Congressional amendment to section 7 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which already imposes registration and reporting requirements upon producers of pesticide products. The Agency is providing a period of 6 months for compliance by producers of active ingredients after the effective date of this rule.

EFFECTIVE DATE: This rule will become effective upon publication in the **Federal Register** of a notice after 60 days of concurrent session of Congress.

FOR FURTHER INFORMATION CONTACT: Phyllis Flaherty, Office of Compliance Monitoring (EN-342), Environmental Protection Agency, Room E710, 401 M Street SW., Washington, DC 20460 (202-382-7825).

SUPPLEMENTARY INFORMATION: Public reporting burden for this collection of information is estimated to average 1.08 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM-223, U.S. Environmental Protection Agency, 401 M Street SW., Washington, DC 20460; and to the Office of Information and Regulatory Affairs, Office of Management and Budget, Washington, DC 20503.

I. Background

FIFRA section 7 requires producers of pesticides and devices to register their producing establishments and file annual reports of pesticide production. In 1978, FIFRA section 7 was amended to add a requirement that producers of the active ingredients, incorporated into pesticides, also register their establishments and file annual production reports. This final rule expands the establishment registration and reporting requirement found in the current regulation to include active ingredient producers. Requirements for establishment registration and production reports are codified in 40 CFR Part 167.

II. Proposed Regulation

EPA issued a proposed rule which was published in the **Federal Register** of March 25, 1987 (52 FR 9504), to implement the 1978 amendment to section 7 of FIFRA. The final rule responds to comments on that proposal.

The treatment of multiple-use active ingredient chemicals (i.e., chemicals which have both pesticidal and non-pesticidal uses) was the primary issue facing EPA in implementing the congressional change of requiring registration of establishments producing active ingredients.

In some instances, the primary uses of such multiple-use chemicals are non-pesticidal (such as with xylene, arsenic, and copper sulfate). This situation raises a number of problems in implementing the congressional change. First, a producer might not be aware that his multiple-use chemical is being used as a pesticide. If he does know, he may not know exactly what volume of his chemical production is used as a pesticide active ingredient, as opposed to a non-pesticidal use.

In 1980, the Agency intended to address these problems by proposing the following requirements:

1. Each active ingredient producer must register his establishment and report the entire production of any chemical which has pesticidal use.

2. Each pesticide producer must notify the suppliers of any active ingredient used in his product if the ingredient is not already registered as a pesticide by the supplier.

3. Both pesticide producers and active ingredient producers must keep records of the notices described in item 2 above.

However, because of extensive comments from producers of large quantities of multiple-use chemicals, the Agency published a reproposal. This reproposal clarified the establishment registration requirement by requiring a producer to report only that production of an active ingredient for which the producer had actual or constructive knowledge that these active ingredients were used in the production of pesticide products. The reproposal also deleted the establishment registration requirement for custom blenders as well as several minor changes clarifying the requirements for pesticide-producing establishments.

III. Discussion

In response to comments received during the comment period for EPA's proposal of March 25, 1987 (52 FR 9504), EPA is promulgating the rule with only minor modifications.

1. Minor Changes to the Rule

(a) The phrase "market produced for (domestic, foreign, etc.)" had been inadvertently deleted from the definition of "type of pesticide" at § 167.3(j). This error was corrected.

(b) One comment suggested that companies which own establishments in EPA Regions that are different from the EPA Region containing the company headquarters only have the company headquarters submit establishment registration applications to its respective EPA Regional office. This comment was incorporated.

(c) Another comment requested that companies which change ownership or address be allowed to report such change on letterhead stationery as well as the form required by § 167.20(e). This comment was incorporated.

(d) A suggestion was made to include a statement clarifying the fact that while the Agency will have reporting forms available and the Agency does supply them to companies each year as a courtesy, the ultimate responsibility to obtain, complete, and submit the forms provided by the Agency is the company's. This comment was incorporated.

(e) Finally, it was suggested that the date of submission of the Annual Report required by § 167.85(c) be changed from February 28, as was suggested in comments responding to the first proposal, to March 1. The date was changed.

2. Who Must Register

Any producer who has actual or constructive knowledge that a substance he produces is used or intended for use as an active ingredient in the manufacture of a pesticide, will be required to register his establishment(s). Also, all establishments which produce any pesticide, device, or active ingredient subject to this provision must be registered. This includes biotechnology pesticide products.

3. What Quantities of Active Ingredient Must Be Reported

A producer is subject to FIFRA requirements if he intends that the substance produced be used as a pesticide or in the formulation of a

pesticide product. However, at the level of active ingredient production, a producer may not intend his substance to be used in a pesticide, but he may produce it with knowledge that it has pesticidal uses. The Agency, therefore, considers substances affected by this rule to be those produced, sold or distributed with the knowledge, actual or constructive, that they are used or intended for use as an active ingredient in the production of a pesticide.

The rule requires active ingredient producers to report only the amount of substance as to which the producer has actual or constructive knowledge of its use or intended use as an active ingredient in the manufacture of a pesticide.

The Agency will use an objective standard in determining whether a producer knows his substance is being used as an active ingredient for pesticides, and which amount of the substance is being used for those purposes. A producer will be considered to know that his substance is used for pesticidal purposes if a reasonable person in the position of an active ingredient producer would be considered to know of that use. Benchmarks of knowledge will include promotional claims and advertising, common knowledge of the general business of the formulator, and the length of the chain of production and distribution, that is, the commercial distance from the substance producer to the ultimate pesticide producer.

4. How to Report

The reports required by § 167.85(c) must be made by submitting to the Agency a form entitled "Pesticides Report," EPA Form 3540–16. The term "pesticide," as used in the form and in the instructions to the form, shall be read also to include pesticide products, devices, and active ingredients.

5. How to Register

Any person who wishes to register an establishment must complete and submit to the Agency a form entitled "Application for Registration of Pesticide-Producing Establishments," EPA Form 3540–8. Any establishment which has not previously been required to register and is not currently registered as a producing establishment must apply for establishment registration by submitting an application within 180 days after the effective date of this regulation.

6. Other Changes to the Rule

The language of Part 167 was rewritten in the proposed amendment to clarify the regulations. Proposed changes in the language of the rule were made to reflect more accurately the existing practices of the Agency. However, except for those changes explained above which were made to include the active ingredient producers in the regulatory scheme, these changes do not reflect an substantive change in the requirements to register estabishments and/or report production with the exception of deleting the registration and reporting requirement for custom blenders.

This rule no longer requires custom blenders to register their establishments and report production. Custom blenders provide the service of mixing pesticides to a customer's specifications. The custom blend can be a pesticide(s)/fertilizer(s) mixture, a mixture of end-use formulations derived from registered pesticides, or a mixture of animal feed and feed-through pesticide(s). Under the Agency's May 10, 1982 FIFRA Compliance Program Policy No. 3.4 entitled "Custom Blenders," the Agency determined that the registration of custom blend pesticides would not be necessary to fulfill the intent of FIFRA. Moreover, the May 10, 1982 FIFRA Compliance Policy No. 7.1, entitled "Custom Blenders," states that custom blenders are not required to report establishment production. Registration of custom blending establishments was required to allow the Agency to schedule inspections and trace pesticides which are contaminated or adulterated. The Agency no longer uses the registration of custom blending establishments as the targetting method for conducting inspections for contamination or adulteration of a pesticide. As a result of deleting the registration requirement for custom blenders the paperwork burden for such establishments will be reduced. Furthermore, since registrants keep or are required to keep records regarding sales, the Agency believes it can effectively locate such products without custom blending establishments being registered.

The Agency believes that the authority under section 8 of FIFRA will allow the Agency to detect and track the sale and distribution of products that are contaminated or adulterated. Custom blenders remains subject to the provisions of FIFRA section 8 as well as all the requirements relating to the proper use of pesticides including transport, storage and disposal. The Agency believes the public will be adequately protected without the registration and reporting requirements by custom blenders. Therefore, the Agency exempts producers of custom-blended pesticides from the requirement of establishment registration and reporting of production under the authority of FIFRA section 25(b).

This exemption also applies to custom blenders of animal feed-through pesticides, especially those who blend feed-through larvicide products. Establishments which custom blend feed-through pesticides, and no other pesticides, are not currently registered as pesticide-producing establishments. This is due to an interim decision made by the Agency, that the final determination as to whether or not these establishments would be required to register would be made when the Agency issued amended section 7 regulations. The interim decision was based on the issue of dual jurisdiction between the Agency under FIFRA section 7 and the Food and Drug Administration under the Current Good Manufacturing Practice regulation (21 CFR Part 225).

Elimination of the establishment registration and reporting requirements for custom blenders of animal feed-through pesticides affects approximately 10,000 establishments, most of which are not currently registered with the Agency.

The change in date effecting the submittal of annual reports will provide adequate time for the forms to be sent to and received by the Agency. Section 167.85(d) reflects this revision.

This rule also permits producers to report changes in ownership or address of an establishment on the same form as the registration of establishments form (EPA Form 3540–8) or on company letterhead stationary. This is consistent with current Agency practice.

The elimination of establishment registrations for custom blenders caused some concern for States as expressed by some State Pesticide Lead Agency Officials and some Regions. The States expressed concern that the removal of this information from the data base supplied by the Regions could impair their inspection targetting. The Regions were concerned that some "custom blenders" are actually producing pesticides and as such should be reporting production under section 7. The Agency understands this concern and has agreed to:

(1) Maintain a listing of all the currently registered custom blending establishments as of the effective date of the regulations.

(2) Draft a letter to be included with the 1988 annual solicitation for pesticide production reports stating that custom blenders must evaluate their production status, and if they produce pesticides as outlined in section 2(w) of FIFRA, they

must notify the Regional Office. Otherwise they are removed from the Agency's producing establishment list. However, establishments producing registered pesticides and providing custom blending services are still required to maintain their establishment registration and report production of registered pesticide products.

The last change to Part 167 was to eliminate the labeling requirement at § 167.4 which discussed establishment number, placement and designation of the EPA establishment number. These labeling requirements are now found at § 162.10(f).

IV. Related Regulation

This rule should be read in conjunction with 40 CFR Part 169—Books and Records of Pesticide Production and Distribution, the latest amendment to which was published in the **Federal Register** of August 15, 1980 (45 FR 54338).

V. Conversion Table

For the convenience of the user, the following table shows the relationship between the old and new CFR section numbers.

Old Section	New Section
167.1	167.3
167.2	167.20
167.3	167.20
167.5	167.85
	167.90

Section 167.4 has been deleted since it is covered by § 162.10(f) of the *Labeling requirements.*

VI. Statutory Requirements

The Secretary of Agriculture has reviewed this rule as required by FIFRA section 25(a)(2)(A) and the Scientific Advisory Panel has waived review of this rule as required by FIFRA section 25(d).

VII. Other Regulatory Requirements

A. Executive Order 12291

Under Executive Order 12291, the Agency must judge whether a rule is "Major" and therefore subject to the requirement of a Regulatory Impact Analysis. The Agency has determined that this rule is not major. Although it amends an existing rule by adding as well as deleting some respondents to registration and reporting requirements, it will not;

1. Have an annual effect on the economy of $100 million or more.

2. Increase costs to consumers, industry, or Government.

3. Have a significant adverse effect on competition, employment, investment, productivity, or innovation.

This rule was submitted to the Office of Management and Budget for review as required by Executive Order 12291.

B. Regulatory Flexibility Act

Under section 605(b) of the Regulatory Flexibility Act, 5 U.S.C. 605(b), the Administrator may certify that a final rule will not, if promulgated, have a significant impact on a substantial number of small entities and, therefore, does not require a regulatory flexibility analysis.

This rule will require those establishments involved in producing multiple-use chemicals, where the manufacturers intend or have constructive knowledge that such chemicals are used as active ingredients in the production of pesticides, to register their establishments and report production on an annual basis under section 7 of FIFRA. The Agency believes that most establishments which produce multiple-use substances are larger businesses, which may already be registered. Additionally, it removes the requirement to register custom blender establishments.

Therefore, I certify that this rule will not have a significant economic impact on a substantial number of small entities.

C. Paperwork Reduction Act

The Office of Management and Budget (OMB) has approved the information collection requirements contained in this rule under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.* and has assigned OMB control numbers 2070–0045 and 2070–0078.

Public reporting burden for this collection of information is estimated to average 1.08 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM–223, U.S. Environmental Protection Agency, 401 M St. SW., Washington, DC 20460; and to the Office of Information and Regulatory Affairs, Office of Management and Budget, Washington, DC 20503.

List of Subjects in 40 CFR Part 167

Pesticides, Reporting and recordkeeping requirements, Establishment registration.

Dated: August 26, 1988.

John A. Moore,

Acting Administrator.

Therefore, 40 CFR Chapter I is amended by revising Part 167 to read as follows:

PART 167—REGISTRATION OF PESTICIDE AND ACTIVE INGREDIENT PRODUCING ESTABLISHMENTS, SUBMISSION OF PESTICIDE REPORTS

Subpart A—General Provisions

Sec.

167.3 Definitions.

Subpart B—Registration Requirements

167.20 Establishments requiring registration.

Subparts C and D—[Reserved]

Subpart E—Recordkeeping and Reporting Requirements

167.85 Reporting requirements.

167.90 Where to obtain and submit forms.

Authority: 7 U.S.C. 136 (e) and (w).

Subpart A—General Provisions

§ 167.3 Definitions.

Terms used in this part shall have the meanings set forth for such terms in the Federal Insecticide, Fungicide, and Rodenticide Act. In addition, when used in this part, the following terms shall have the meanings stated below:

"Act" means the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, 7 U.S.C. 136 *et seq.*

"Amount of pesticidal product" means quantity, expressed in weight or volume of the product, and is to be reported in pounds for solid or semi-solid pesticides and active ingredients or gallons for liquid pesticides and active ingredients, or number of individual retail units for devices.

"Current production" [sales or distribution] means amount of planned production in the calendar year in which the pesticides report is submitted, including new pesticidal products not previously sold or distributed.

"Custom blender" means any establishment which provides the service of mixing pesticides to a customer's specifications, usually a pesticide(s)-fertilizer(s), pesticide-pesticide, or a pesticide-animal feed mixture, when: (1) The blend is prepared to the order of the customer and is not held in inventory by the blender; (2) the blend is to be used on the customer's property (including leased or rented

property); (3) the pesticide(s) used in the blend bears end-use labeling directions which do not prohibit use of the product in such a blend; (4) the blend is prepared from registered pesticides; (b) the blend is delivered to the end-user along with a copy of the end-use labeling of each pesticide used in the blend and a statement specifying the composition of mixture; and (6) no other pesticide production activity is performed at the establishment.

"Device" means any device or class of devices as defined by the Act and determined by the Administrator pursuant to section 25(c) to be subject to the provisions of section 7 of the Act.

"Establishment" means any site where a pesticidal product, active ingredient, or device is produced, regardless of whether such site is independently owned or operated, and regardless of whether such site is domestic and producing a pesticidal product for export only, or whether the site is foreign and producing any pesticidal product for import into the United States.

"Past year" means the calendar year immediately prior to that in which the report is submitted.

"Pesticidal product" means a pesticide, active ingredient, or device.

"Pesticidal product report" means information showing the types and amounts of pesticidal products which were: (1) Produced in the past calendar year; (2) produced in the current calendar year; and, (3) sold or distributed in the past calendar year. For active ingredients, the pesticidal product report must include information on the types and amounts of an active ingredient for which there is actual or constructive knowledge of its use or intended use as a pesticide. This pesticidal product report also pertains to those products produced for export only which must also be reported. A positive or a negative annual report is required in order to maintain registration for the establishment.

"Produce" means to manufacture, prepare, propagate, compound, or process any pesticide, including any pesticide produced pursuant to section 5 of the Act, any active ingredient or device, or to package, repackage, label, relabel, or otherwise change the container of any pesticide or device.

"Producer" means any person, as defined by the Act, who produces any pesticide, active ingredient, or device (including packaging, repackaging, labeling and relabeling).

"Sold or distributed" means the aggregate amount of a pesticidal product released for shipment by the establishment in which the pesticidal product was produced.

"Type of pesticidal product" refers to each individual product as identified by: the product name; EPA Registration Number (or EPA File Symbol, if any, for planned products, or Experimental Permit Number, if the pesticide is produced under an Experimental Use Permit); active ingredients; production type (technical, formulation, repackaging, etc.); and, market for which the product was produced (domestic, foreign, etc.). In cases where a pesticide is not registered, registration is not applied for, or the pesticide is not produced under an Experimental Use Permit, the term shall also include the chemical formulation.

Subpart B—Registration Requirements

§ 167.20 Establishments requiring registration.

(a) *Who must register.* (1) Any establishment where a pesticidal product is produced must be registered with the Agency. This requirement does not apply to custom blenders as defined in this part.

(2) Any establishment where a substance is produced must be registered with the Agency if the producer intends the substance to be used as an active ingredient of a pesticide, or has actual or constructive knowledge that the substance will be used by any person as an active ingredient of a pesticide.

(3) Any domestic establishment producing a pesticidal product for export, or any unregistered pesticide, or any foreign establishment producing a pesticidal product for import into the United States must be registered. Also, any establishment, either foreign or domestic, which produces a pesticidal product for use under an Experimental Use Permit, FIFRA section 18 Emergency Exemption or section 24(c) Special Local Needs registration, must be registered.

(b) *Information required.* An applicant for establishment registration must submit the following information:

(1) Name and address of the company.

(2) The type of ownership (individual, partnership, cooperative association, corporation, or any organized group of persons whether incorporated or not).

(3) The name and address of each producing establishment for which registration is sought.

(c) *When to apply.* An application for establishment registration must be submitted, and an establishment registration number must be assigned by the Agency, before any production may occur at an establishment. In the case of an establishment which has not previously been required to be registered and is not currently registered, the producer must apply for establishment registration by submitting an application within 180 days after the effective date of this regulation.

(d) *Assignment of establishment registration number.* The Agency will return incomplete or inaccurately completed applications to the applicant. If the application is complete and accurate, the Agency will register the establishment and assign a registration number to the establishment. The establishment registration number will be entered on the application, and a copy of the application will be returned to the applicant.

(e) *Amendment.* If at any time after the first report there is a change in the information required to be submitted under paragraph (b) of this section, that new information must be reported to EPA, in writing on letterhead stationery or on forms supplied by the Agency, within 30 days after such change occurs.

(f) *Duration of registration.* Establishment registration will remain effective provided pesticide reports are submitted annually pursuant to the requirements of this part. Failure to submit a report may result in termination of establishment registration, civil and/or criminal penalty assessments.

(Approved by the Office of Management and Budget under control number 2070–0045)

Subparts C and D—[Reserved]

Subpart E—Recordkeeping and Reporting Requirements

§ 167.85 Reporting requirements.

(a) *Who must report.* Each producer operating an establishment must submit the reports required by this section concerning any pesticide, active ingredient, or device produced at each establishment. Custom blenders are not required to report production to the Agency.

(b) *Information required.* The pesticide report shall include the following: (1) Name and address of the establishment; (2) amount of each pesticidal product: (i) Produced during the past year; (ii) sold or distributed during the past year; (iii) estimated to be produced during the current year. The report shall only include those pesticidal products actually produced at the reporting establishment. Reports submitted by foreign-producing establishments shall cover only those pesticidal products exported to the United States.

(c) *How to report.* The reports required by this section must be made on forms supplied by the Agency. It is the ultimate responsibility of companies to obtain, complete, and submit the form each year.

(d) *When to report.* A producer operating an establishment must submit an initial report no later than 30 days after the first registration of each establishment the producer operates. Thereafter, the producer must submit an annual report on or before March 1 of each year, even if the producer has produced no pesticidal product for that reporting year.

(Approved by the Office of Management and Budget under control number 2070-0078)

§ 167.90 Where to obtain and submit forms.

(a) *Where to obtain forms.* Any person may obtain blank forms for the applications and reports required by this part from any EPA Regional Office, or from the address listed in paragraph (b) of this section.

(b) *Where to submit applications and reports.* Each producer operating an establishment, with the exception of those establishments not found at the same location as their company headquarters, must submit applications and reports required by this Part to the EPA Regional Office which serves the area where the establishment is located. The list of Regional Office addresses is found in 40 CFR 1.7. Applications and reports for those establishments not found at the same location as their company headquarters to be submitted by the company headquarters to the Regional Office having jurisdiction over the State in which the company headquarters is located. A foreign producer who exports any pesticide product, device, or active ingredient to the United States must submit all applications and reports to:

U.S. Environmental Protection Agency, Office of Compliance Monitoring (EN-342), 401 M Street SW., Washington, DC 20460.

[FR Doc. 88-20320 Filed 9-7-88; 8:45 am]

BILLING CODE 6560-50-M