## IN VITRO NUCLEAR MEDICINE

# Two Radioimmunoassays Compared with Isoenzyme Electrophoresis for the Detection of Serum Creatine Kinase-MB in Acute Myocardial Infarction

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**We have evaluated two commercial radioimmunoassay (RIA) reagent kits for the estimation of the MB isoenzyme of creatine kinase (CK). Although both methods use CK-B antisera and radioiodinated CK-B, one ("M" for Mallinckrodt) uses hybridized CK-MB for calibration, while the other ("NMS" for Nuclear Medical Systems) uses CK-B. Both assays provide adequate sensitivity, precision, and specificity for the estimation of serum CK-MB.**

**Ninety-nine patients admitted consecutively to our coronary care unit were studied. Apparent CK-MB was measured by both RIAs and results compared with CK-MB enzymatic activity after electrophoresis (E). CK-MB was elevated, as judged by E and by M, in all of 42 patients with acute myocardial infarction (AMI), and in 40 of the 42 by NMS. Of the 57 patients who did not have an AMI, eight had elevated CK-MB by E, 16 by M, and 25 by NMS. Patients with persistently elevated apparent CK-MB concentrations not associated with AMI were identified by M and by NMS, but not by E. The ability to differentiate AMI from no infarction in patients was best with E, and was not satisfactory by NMS. Although the detection of AMI by M equaled that by E, the large number of apparent false-positive results hindered the clinical application of RIA CK-MB measurements.**

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Detection of the heart isoenzyme of creatine kinase (CK-MB) in the blood is the most important laboratory criterion for establishing the diagnosis of acute myocardial infarction (*1–5*). Classically, the detection and quantitation of CK isoenzymes depended upon their physical separation by electrophoresis or ion-exchange chromatography followed by the demonstration of enzymatic activity after the addition of suitable substrate (*6*). More recently, radioimmunoassay methods using antisera directed against CK-B have been described (*7–10*). Two such radioimmunoassays, one using CK-BB as the calibrator, the other employing hybridized CK-MB, are commercially available. We have measured the apparent concentrations in the sera of patients admitted to our coronary care unit using these two commercial kits in order to assess their clinical efficacy.

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### METHODS

**Patients studied.** Ninety-nine patients admitted consecutively to the coronary care unit of our hospital for suspected acute myocardial infarction provided the patient population for this report. Eighty-nine patients came to the emergency room shortly after onset of symptoms. Ten patients had symptoms of longer than 24 hr duration. Blood specimens were routinely obtained shortly after admission and again after 12, 24, and 48 hr. Additional specimens were obtained as clinically indicated. Creatine kinase isoenzyme MB (CK-MB) was measured in all samples by electrophoresis and by two radioimmunoassays. Serial electrocardiograms were

obtained on admission and daily for several days. The clinical and laboratory findings of all patients were reviewed.

CK-MB was also measured by radioimmunoassay in sera obtained from 46 ambulatory patients with no known heart disease.

**Sample collection and CK stability.** Serum was separated from red cells immediately and stored at 4 °C before electrophoretic separation and quantitation of isoenzymes (within the same day). If measurements by radioimmunoassay were not made within the same day, serum samples were frozen until the time of assay (within 2 days of collection). The stability of immunoreactive CK-MB stored at −20 °C or subjected to repeated freeze-thaw cycles was evaluated. CK-MB was measured in 20 samples by radioimmunoassay (Mallinckrodt) on the day they were drawn, after which they were again frozen. The samples were then thawed, assayed, and frozen again daily for 3 days. Sera studied had CK-MB concentrations of 18–139 ng/ml. Eighteen sera were reassayed after storage for 4 mo at −20 °C (Nuclear Medical Systems). After storage at −20 °C for one year, apparent concentrations of CK-MB were measured again by both RIA kits.

**Radioimmunoassays.** CK-MB was measured by two commercial radioimmunoassay reagent kits: Mallinckrodt Inc., St. Louis, MO (M) and Nuclear Medical Systems, Newport Beach, CA (NMS). The manufacturers' protocols were used without modification.

Antisera in both systems were raised in rabbits immunized with CK-B extracted from human brain tissue. The M system uses hybridized human CK-MB for calibration, prepared by the reassociation of M and B subunits obtained by the dissociation of CK-MM and CK-BB. The NMS system is a homologous system using CK-B and radioiodinated CK-B for calibration. Either assay may be completed within 3–4 hr.

The standard dose-response curves for both the M and the NMS assays expressed as logit % (bound activity over bound activity at zero concentration) versus log calibrator concentration (ng/ml) were found to be linear. A computer program using a weighted least-squares regression was used to estimate control or patients' unknown serum CK-MB concentrations.

**Electrophoresis.** The CK isoenzymes present in patient sera samples were separated by electrophoresis on agarose.* After subsequent incubation with substrate, the isoenzymes were identified under ultraviolet light and quantitated using a densitometer. Total serum CK activity was estimated by measuring NADH production at 340 nm on a centrifugal analyzer using commercial reagents.†

**Myocardial infarction.** The presence or absence of myocardial infarction was determined by the clinician, based on the patient's clinical findings and course, serial electrocardiographic changes, pyrophosphate scans, and serum myocardial enzyme measurements, principally the presence or absence of CK-MB. CK-MB measurements by radioimmunoassay were not reported to the clinician, and therefore did not influence the diagnosis. The radioimmunoassay measurements were correlated with the clinical and laboratory data.

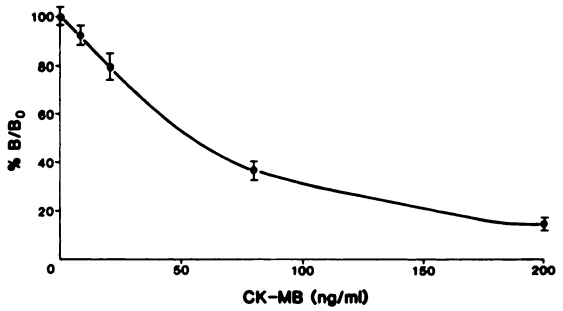


**FIG. 1.** Representative CK-MB standard curve for the M assay.

## RESULTS

**CK stability.** No significant differences in apparent CK-MB concentrations measured by either RIA were observed when patient sera were subjected to repeated freeze-thaw cycles or were stored frozen for up to 4 mo. After one year's storage at −20 °C, however, CK concentrations were found to be markedly decreased by one assay (NMS), but increased by the other (M).

**Radioimmunoassays.** A representative standard curve obtained with the M assay is shown in Fig. 1. Initial (zero standard) binding was 24–33%, sensitivity ($B/B_0$ = 90%) was 10 ng/ml, and nonspecific binding (NSB) was 3–5% of the total activity (TA) both in calibrators and in patient sera. Precision (coefficient of variation) for three control pools (7.6–62 ng/ml), provided by the manufacturer and used during the course of our study, was 5.0–10.4% within assay runs and 6.7–15% between runs.

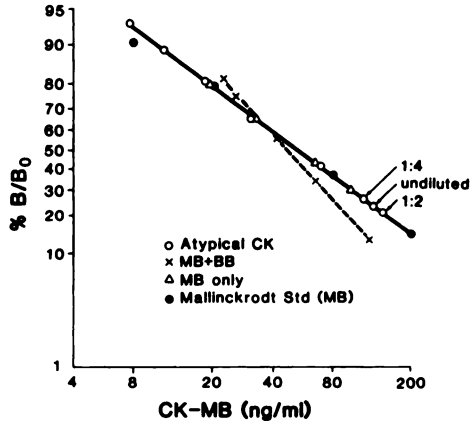


**FIG. 2.** Displacement observed with dilutions of patient sera containing CK-BB, atypical CK, and CK-MB, compared with the M standard curve.

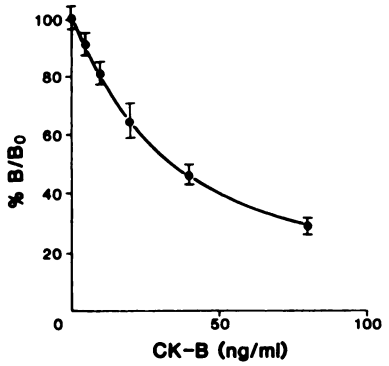


FIG. 3. Representative CK-B standard curve for the NMS assay.

Recoveries of the M hybridized CK-MB calibrator added to human serum with a low initial concentration of CK-MB were 89-100%. Dilutions of some sera containing CK-MB detected electrophoretically paralleled the standard curve (Fig. 2). Frequently, an initial 1:2 dilution resulted in a higher dose estimate, with parallel results after the initial serum dilution. Dilution of serum containing both CK-MB and CK-BB did not, however, result in a parallel displacement curve. Dilutions of serum containing atypically migrating CK (bifid M) resulted in a higher apparent dose estimate when diluted 1:2. Subsequent dilutions then paralleled the standard curve. One patient was encountered during the course of this study with CK-MM concentrations in excess of 24,000 ng/ml. Serum obtained from this patient resulted in minimal displacement in the M assay. No further studies of specificity were carried out.

A representative standard curve obtained with the NMS assay is shown in Fig. 3. Initial binding was 26-28%, sensitivity was 2.5 ng/ml, and NSB was 3-5% of the TA in both calibrators and patient sera. Within- and between-assay run precision for two control pools (4.9 and 31 ng/ml), provided by the manufacturer and used during the course of our study, were 14 and 6.5% (CV) and 16 and 5.6%, respectively. Recoveries of the NMS

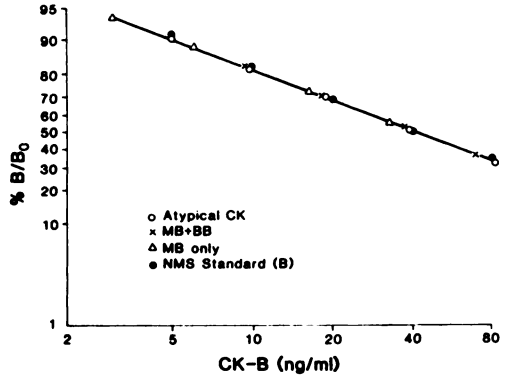


FIG. 4. Displacement observed with dilutions of patient sera containing CK-BB, atypical CK, and CK-MB, compared with the NMS standard curve.

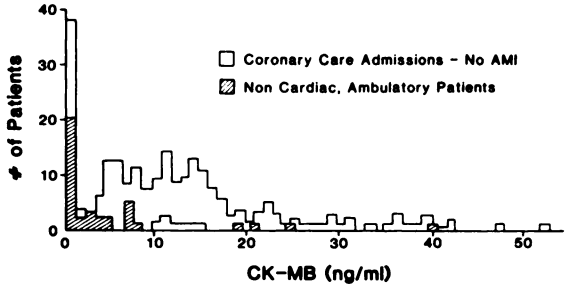


FIG. 5. Apparent CK-MB concentrations observed in noninfarcted patients with the M assay.

CK-B calibrator added to human serum with a low initial CK-MB concentration were 89-109%. Dilutions of sera containing CK-MB, as well as serum containing CK-MB and CK-BB and serum containing an atypical CK, all resulted in displacement parallel to the CK-B calibration curve (Fig. 4). Minimal displacement was observed when a serum sample with greater than 24,000 ng/ml CK-MM was tested. No further studies of specificity were carried out.

**Patient studies.** Forty-two patients were classified as having had an acute myocardial infarction (AMI), leaving 57 patients who had not.

**Noninfarcted patients.** The distribution of results in ambulatory noncardiac patients and those obtained in the 57 noninfarcted patients admitted to the Coronary Care Unit is shown in Fig. 5 for the M assay and in Fig. 6 for the NMS. Significantly lower ($p < 0.01$, by Student's $t$-test) results were observed in the ambulatory patients with both radioimmunoassays. On the basis of these results, apparent CK-MB values >30 ng/ml were considered abnormally elevated by the M assay and >12.5 ng/ml elevated by the NMS assay.

**Myocardial infarct group.** Table 1 summarizes the CK-MB results in 42 patients with AMI. The temporal detection of CK-MB was similar for all three assays (radioimmunoassays, electrophoresis).

The clinical problems in patients with apparent false-positive CK-MB results by the two radioimmunoassay procedures are summarized in Table 2. The majority of these patients had had cardiac episodes but

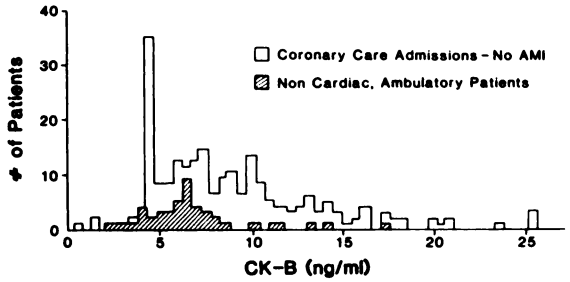


FIG. 6. Apparent CK-MB concentrations observed in noninfarcted patients with the NMS assay.

**TABLE 1. CK-MB RESULTS BY RIA (M, NMS) AND ELECTROPHORESIS (E) IN 99 PATIENTS SUSPECTED OF HAVING AN ACUTE MYOCARDIAL INFARCTION (AMI)**

| | M | | NMS | | E | |
|---|---|---|---|---|---|---|
| AMI | Neg | Pos | Neg | Pos | Neg | Pos |
| Yes (42) | 0 | 42 | 2 | 40* | 0 | 42 |
| No (57) | 41 | 16 | 32 | 25 | 49 | 8 |

* Four patients had inappropriate persistent CK-MB elevations after CK-MB returned to normal by both the M-RIA and E. Six patients had maximum CK-MB concentrations between 12.5 and 15 ng/ml.

were not believed by their physicians to have had clinically significant myocardial infarction. CK-MB concentrations above the decision threshold, not varying upon subsequent testing, were encountered in a small number of patients (Table 3). Concentrations as high as 200 ng/ml (M) were seen.

Renal insufficiency did not result in increases in CK-MB as measured by radioimmunoassay (Table 4). Because CK-BB has been reported in association with neoplasms and may be present after central nervous system insults, we examined our results in patients with these problems (Table 4). We detected no inappropriate increases in CK-MB in any of these patients.

## DISCUSSION

Creatinine kinase, the enzyme catalyzing the reversible phosphorylation of creatine by adenosinetriphosphate (ATP), is ubiquitously present in human tissues. The enzyme is composed of two monomeric protein subunits, designated M and B, which combine to form three dimers—MM, MB, and BB. Skeletal muscle is the major source of CK-MM, although smaller quantities are found in virtually all body organs including the heart (*11,12*). Although CK-BB is the only isoenzyme of CK present in the brain, it is also widely present in most body tissues (*11–13*). The principal source of CK-MB is heart muscle; only minor amounts of CK-MB are present elsewhere (*12,13*). The presence of CK-MB in the blood, therefore, is virtually specific for cardiac injury, whereas CK-MM and CK-BB are both relatively nonspecific tissue markers.

Since all three CK isoenzymes catalyze the same reaction, they must be physically separated before CK-MB can be measured by methods dependent upon the demonstration of enzymatic activity (*5,6,14,15*).

The development of radioimmunoassays suitable for the detection and quantitation of CK-MB in the presence of CK-MM depends upon the antiserum specificity. Since the detection of CK-BB in normal human sera following electrophoresis is unusual, antisera directed against CK-B appeared to provide this requisite specificity. CK-BB suitable for immunization is easily extracted from human brain tissue (*7*). Most investigators have utilized the same CK-BB for radioiodine labeling. The introduction of iodine directly into CK-BB by usual oxidative reactions results in marked loss of enzymatic

**TABLE 2. CLINICAL PROBLEMS IN PATIENTS WITH POSITIVE CK-MB BY RIA WHO HAD NOT HAD AMI**

| | Number of patients | |
|---|---|---|
| | M | NMS |
| Coronary artery disease/angina | 4 | 9 |
| Cardiac arrest/resuscitation | 4 | 2 |
| Congestive heart failure | 3 | 4 |
| Arrhythmia | — | 1 |
| After coronary artery bypass (10 d) | 1 | 1 |
| Mitral valve prolapse | — | 2 |
| Hypertension | 1 | 1 |
| Carbon monoxide poisoning | 1 | 1 |
| Cholecystitis/lithiasis | 1 | 2 |
| Cholelithiasis/atypical CK | 1 | 1 |
| Chest wall pain | — | 1 |
| | 16/57 | 25/57 |

**TABLE 3. INAPPROPRIATE, PERSISTENTLY POSITIVE CK-RIA RESULTS**

| AMI | M | NMS |
|---|---|---|
| Yes | 0/42 | 4/42 |
| No | 6*/57 | 7/57 |

* Three also persistently elevated by NMS.

**TABLE 4. NONCARDIAC MEDICAL PROBLEMS**

| | Number of patients with CK-MB | |
|---|---|---|
| | Pos | Neg |
| Uremia | | |
| creat. >3 mg/dl | 2 | 2 |
| creat. 1.5–3 mg/dl | 22 | 10 |
| Cerebrovascular disease* | 2 | 1 |
| Cancer | | |
| Prostate | 3 | 1 |
| Lung | 1 | 1 |
| Other | 1 | 1 |

* 2, recent cerebrovascular accidents; 1, Parkinson's disease.

activity, probably due to oxidation of an essential sulfhydryl group (*7,8*). Preservation of enzymatic activity is not a necessary requisite for a successful assay, and CK labeled directly has been used successfully in radioimmunoassays (*9,16*). Iodine-125 may also be introduced into appropriate aromatic compounds which, when conjugated through amino groups of the CK proteins, results in radiolabeled CK retaining enzymatic activity (*7,8*).

Most radioimmunoassays have been calibrated using CK-BB extracted from brain tissue. The CK dimers may, however, be disassociated by 8 *M* urea with loss of enzymatic activity (*17*). Subsequent addition of thiols results in reassociation (hybridization) with partial restoration of activity (*18,19*). Hybridized CK-MB, prepared from disassociated CK-MM and CK-BB, was used in one of the assays we studied (M).

Radioimmunoassay of CK-MB represents a significant departure from other methods because it measures the apparent *mass* of proteins recognized by the antibody. This measurement is related to biologic activity only if the immunologic determinants happen to coincide with the sites necessary for enzymatic activity. In the radioimmunoassay for detection of CK-MB initially described by Roberts et al., immunoassayable activity paralleled enzymatic activity (*7*) that is rapidly lost from stored samples (*12,18,20*). More commonly, as in the two assays we studied, immunoassayable activity is not lost with repeated freezing and thawing or after storage at −20 °C for several months (*10*). We did observe a decline in the apparent CK-MB concentration in specimens stored frozen for one year as measured by one assay (NMS), and an increase as measured by the other (M). This finding suggests that conformational changes or degradation associated with long-term storage (months) is variably recognized by antisera currently used to quantitate CK-MB. In a radioimmunoassay recently described by Burnam, there was an inverse relationship between the immunoassayable and CK enzymatic activities (*16*).

Unlike earlier assays, apparent CK-MB is normally detected in the blood by radioimmunoassay. A decision threshold must therefore be selected to differentiate normal from abnormally elevated concentrations of CK-MB. We were able to differentiate abnormal from normal results more easily with the assay using hybridized CK-MB (M) (Fig. 5) than we could with the homologous CK-B system (NMS) (Fig. 6). For the clinical question posed ("Has the patient had an acute myocardial infarction?"), clinical sensitivity approaching 100% is desirable. High sensitivity was achieved with fewer apparent false-positive results with the M assay than with the NMS (Table 1). In order to avoid choosing a decision threshold for the NMS assay resulting in an even more unacceptably high number of false-positive patients, we accepted two false-negative patients and six other infarct patients with only marginally elevated apparent CK-MB concentrations.

Dilution of patient sera produced higher apparent CK-MB concentrations for many sera measured in the M assay system. This is perhaps not surprising, since the calibrator used differed from the labeled ligand (CK-B) and probably also differed from native CK-MB in its immunoreactivity. In addition, dilutions of serum containing elevated CK-BB suggest that the M antiserum has a higher affinity for CK-BB than for CK-MB, as has been described for other CK-B antisera by other investigators (Fig. 2) (*7,10*). Dilutions of a serum sample containing an atypically migrating CK also produced anomalous results. We did not observe % $B/B_0$ greater than 100% in any patient sera. All serum samples studied demonstrated dilutional parallelism in the homologous CK-B system (NMS). As demonstrated in the M system and by others, this property is not necessarily expected and, unlike that in many other radioimmunoassays, does not necessarily predict greater clinical efficacy (*7,10*).

In this study, the detection of abnormally elevated CK-MB in the blood of patients with AMI by radioimmunoassay equalled the detection by electrophoresis (Table 1). However, many apparently abnormal results were observed in patients believed not to have had myocardial infarction. Because the antisera used in these assays are primarily directed against CK-BB and because the sensitivity (lowest detectable concentration) is greater than that by electrophoresis, previously undetected CK-BB present in the blood from any of a number of potential tissue sources may be the cause of some of the apparent nonspecificity. CK-BB has been detected in hypo- and hyperthermia, neurological disease, acute (but probably not chronic) renal failure, Reye's syndrome, benign prostatic hypertrophy, in pregnant and postpartum patients, and in patients harboring adenocarcinomas (most commonly prostatic) (*5,21–26*). Additionally, CK-MB may be present in patients with dermatomyositis, severe rhabdomyolysis, and Duchenne's muscular dystrophy (*27–30*). In our study we examined the radioimmunoassay results for patients with uremia, cerebrovascular disease, and neoplastic diseases (Table 4). No inappropriate results were observed in these groups of patients.

In most patients with apparent false-positive results, cardiac episodes (congestive heart failure, angina, arrhythmias, cardiopulmonary resuscitation) did occur, and it is possible the radioimmunoassay results reflect subclinical myocardial necrosis (Table 2). We observed similar results with a myoglobin assay (*31*). We identified several patients, rarely reported (*27*), with elevated apparent CK-MB serum concentrations that did not change on subsequent testing (Table 3). This phenomenon was observed most frequently with the homologous CK-B system (NMS), occurring in infarcted as well as noninfarcted patients. This finding may be confusing if

one attempts to distinguish infarcted from noninfarcted patients using either of these assays, and it emphasizes the need for sequential testing. The finding of persistent, elevated apparent CK-MB concentrations suggests that these elevations are unrelated to acute myocardial infarction.

Since all earlier measurements depended on the demonstration of enzymatic activity, little is known of CK production or disposal rates, whether precursor molecular forms exist, or what the metabolic fate of CK may be. Under what conditions the proteins comprising these primarily intracellular enzymes appear in the blood, and whether enzymatically inactive fragments or monometric subunits are also present, are incompletely understood phenomena. Since antibodies used in radioimmunoassays are directed against the CK-B subunit, most investigators assume that CK-MB is detected because of recognition of, or cross-reactivity with, the B subunit (*7,10*). Although it was suggested by Zweig (*32*) that CK-BB appears in the blood after myocardial damage, more recent immunoabsorption experiments using anti-CK-M suggest that this is not likely.‡ Burnam and colleagues have suggested that their assay recognizes an inactive CK-B (*26,33*).

In conclusion, we have examined two commercial radioimmunoassay kits for the estimation of CK-MB. Although assay validation studies suggested that either assay might be clinically applied, we were better able to discriminate normal from abnormal results with the M assay than with the NMS assay. Although clinical sensitivity was excellent, both assays exhibited nonspecificity, the NMS assay more than the M. Although radioimmunoassay offers greater sensitivity and procedural advantages, a greater understanding of the CK-related proteins present in the blood and a more careful definition of antisera recognition characteristics are needed in order to permit application of these assays clinically with confidence.

## FOOTNOTES

* Corning ACI, Corning Medical, Medfield, MA.

† Statzyme CPK-n-1, Worthington Diagnostics, Freehold, NJ.

‡ Zweig MH: The value of CK-BB by RIA as a cardiac and tumor marker. Presented at a meeting of the Clinical Radioassay Society, Miami, FL, April 30, 1981.

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## GREATER NEW YORK CHAPTER/TECHNOLOGIST SECTION SOCIETY OF NUCLEAR MEDICINE ANNUAL SPRING SYMPOSIUM

**April 23-25, 1982** **Bally (Headquarters Hotel) Sands, Claridge** **Atlantic City, New Jersey**

Program Coordinator, Maria DaCosta, along with the Scientific Program Committee Chairperson, Ted Rubel, announce the following plans for the Annual Spring Meeting of the Greater New York Chapter of the Society of Nuclear Medicine:

| Friday | Saturday | Sunday |
|---|---|---|
| Clinical | Computer | Chief Technologist Session |
| Management Symposium | Cardiac | Patient Care |
| Adjunctive Equipment | Instrumentation | |
| | Scientific Papers | |

The program is approved for VOICE credit; submit scientific papers to Maria Da Costa.

The Physician Section will once again be holding its conjoint meeting with technologists on Saturday.

For more information contact:

Maria DaCosta
Andre Meyer Dept. of Physics-Nuclear Medicine
Mt. Sinai Medical Center
One Gustave L. Levy Place
New York, NY 10029

## 10th ANNUAL MEETING BRITISH NUCLEAR MEDICINE SOCIETY

**April 19-21, 1982** **Imperial College** **London, England**

The British Nuclear Medicine Society announces its Tenth Annual Meeting, to be held from April 19-21, 1982 at Imperial College, London.

The program includes review and original presentations, specialist sessions in radiopharmacy and computing, and for technicians. poster sessions and a commercial exhibition.

For further information, contact:

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