Original Article

Comparing diagnostic performance of ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) and ^{99m}Tc-hydrazinonicotinyl-Tyr^3-Octreotide (^{99m}Tc-HYNIC-TOC) in diagnosis and localization of pheochromocytoma and neuroblastoma

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ABSTRACT

Introduction: The present study was aimed to assess the diagnostic performance of the two imaging methods of ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) and ^{99m}Tc-hydrazinonicotinyl-Tyr^3-Octreotide (^{99m}Tc-HYNIC-TOC) in diagnosis and localization of pheochromocytoma and neuroblastoma.

Methods: This study was conducted on 40 consecutive patients with positive pathological results for pheochromocytoma or neuroblastoma. The patients underwent both I-131 ^{131}I-MIBG and octreotide scintigraphies. By using the findings of cytopathology, biomarkers, imaging studies, as well as the results of a six-month follow-up, a composite reference standard (CRS) was defined as the diagnostic gold standard.

Results: Overall comparison of these two agents revealed higher sensitivity for ^{131}I-MIBG than octreotide study both in patient-based analysis (100% vs. 80.9%, respectively), and lesion-based analysis (94.4% vs. 80.56%, respectively). In pheochromocytoma ^{131}I-MIBG and octreotide are both highly sensitive (100%), while ^{131}I-MIBG is more specific (100% vs. 87.5%). In neuroblastoma, ^{131}I-MIBG is more sensitive than octreotide (100% vs. 81.25%).

Conclusion: Our study shows superiority of ^{131}I-MIBG over octreotide scanning in detection of both neuroblastoma and pheochromocytoma lesions. However, a combination of these two diagnostic tools provides more complete information on the nature and the site of lesions. The first suggested study is ^{131}I-MIBG scanning, and if it is not available, or detecting precise location of all lesions is of concern, octreotide scanning can be helpful as a complementary study. Furthermore, in case of octreotide positive lesions, follow-up can be performed with octreotide scan with less radiation burden.

Key words: ^{131}I-MIBG; Somatostatin analog; Octreotide; ^{99m}Tc-HYNIC-TOC; Pheochromocytoma; Neuroblastoma

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INTRODUCTION

Pheochromocytoma is a rare, catecholamine-secreting tumor derived from chromaffin cells and is manifested as a polygenic syndrome in about one-third of affected patients caused by at least 10 gene mutations [1]. Due to excessive catecholamine secretion, pheochromocytoma may precipitate life-threatening hypertension or cardiac arrhythmias [2]. Despite its deleterious nature, it can be curable if diagnosed early. Various guidelines are released by the endocrine societies for the diagnosis and management of pheochromocytoma [3, 4]. Following biochemical studies, imaging assessments including computed tomography (CT), magnetic resonance imaging (MRI), scintigraphy and positron emission tomography (PET) with the different diagnostic performances are performed to localize the disease [5, 6]. A ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) scan is reserved for cases in which a pheochromocytoma is confirmed biochemically, but CT study or MRI does not show the tumor or gives indeterminate results. $^{123/131}$I-MIBG is a substrate for the norepinephrine transporter and concentrates within adrenal or extra-adrenal pheochromocytoma. ^{131}I-MIBG scanning is frequently used in cases of familial pheochromocytoma syndromes, recurrent pheochromocytoma or malignant pheochromocytoma. Estimates of the sensitivity and specificity of $^{123/131}$I-MIBG scanning vary widely. Reported sensitivity ranges from 53-94% and specificity ranges from 82-92% [7-9].

A somatostatin receptor analog, indium-111 pentetreotide, although less sensitive than ^{131}I-MIBG, may be used to visualize those cases of pheochromocytoma that do not concentrate ^{131}I-MIBG. Neuroblastoma is the most common extracranial solid tumor derived as an embryonal malignancy of the sympathetic nervous system arising from neuroblasts. Age, stage, and biological features of tumoral cells are important prognostic factors [10]. Less than half of the neuroblastoma patients are cured, even with the use of high-dose chemotherapy followed by autologous bone marrow or stem cell rescue. Thus, early diagnosis is of utmost importance to reduce adverse consequences of disease. To localize the neuroblastoma and its extension, a CT scan of the primary site is used. In cases of paraspinal masses, MRI aids in determining intraspinal invasion and cord compression. Functional imaging including $^{123/131}$I-MIBG and octreotide scanning has crucial role in diagnosis of this disease. MIBG accumulates in catecholaminergic cells and provides a specific method to identify primary and metastatic disease [11]. Tc-99m/In-111 labeled somatostatin analogs with better imaging characteristics have also been used to diagnose neuroblastoma with/without metastatic lesions [12]. However the diagnostic accuracy of ^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC in diagnosis of pheochromocytoma and neuroblastoma is still uncertain.

The present study aimed to assess the diagnostic performance of these two imaging radiopharmaceuticals in diagnosis and localization of pheochromocytoma and neuroblastoma.

METHODS

This study was conducted on 40 consecutive patients pathologically proven for pheochromocytoma or neuroblastoma tumors referred for imaging studies to our department.

Study population

For each patient, both MIBG and octreotide imaging were performed. The study plan was fully explained to the patients and written informed consent was obtained from all. A checklist including demographic characteristics of the patient, medical condition, disease course, medications, the results of imaging studies and biochemical assessments were completed.

Imaging techniques

Two imaging modalities including ^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC was performed in all patients. To perform somatostatin analog scintigraphy, ^{99m}Tc-HYNIC-TOC (adults: 25 mCi, children: 5-6 mCi) was injected intravenously. Two hours later, whole body planar images were obtained in anterior and posterior projections, using gamma camera (Siemens, symbia T1 SPECT/CT) with matrix size of 256 × 256 and 14 cm/min speed, using a low energy all purpose (LEAP) collimator. Additional imaging was performed with SPECT/CT method from the neck, chest and abdomonopelvic areas, using the matrix size of 128×128.

After completion of ^{99m}Tc-HYNIC-TOC study, ^{131}I-MIBG scanning was performed. For this study, ^{131}I-MIBG (1 mCi) was injected intravenously and imaging was carried out 24 and 72 hours later using gamma camera (Dual Head Genesis) with high energy collimator, in anterior and posterior projections, using matrix size of 64 × 64 and 3 cm/min speed.

When available, cytopathology result was used as the gold standard of the study; otherwise a composite reference standard (CRS) including biomarkers, imaging studies, and the six-month follow-up evaluations was applied. Positive CRS means the presence of disease and negative CRS means the absence of disease. Lesion distribution was categorized as no lesion, single focus, multifocal, and widespread lesions. The intensity of uptake in the lesions was assessed by visual comparison to the liver activity as follows: mild (less than liver uptake), moderate (similar to liver uptake), and severe (higher

than liver uptake). The scans were interpreted by two nuclear medicine specialists, and their common agreement was considered as the final diagnosis.

Statistical analysis

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using t test or Mann-Whitney U test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using chi-square test. To determine the diagnostic value of two imaging procedures in distinguishing the presence or absence of lesions, the sensitivity and specificity of the two scintigraphic methods were calculated using the cross tabulation method and by the specific formula. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

RESULTS

From the total of 40 patients, 19 (47.5%) were female and 21 (52.5%) were male with median age of 6 years (range 2-63 years). Based on pathology report, the overall frequency of neuroblastoma and pheochromocytoma were 29 (72.5%) and 11 (27.5%), respectively. To assess the diagnostic accuracy of the two imaging methods, two approaches including patient-based and lesion-based analysis were used. The results of the study were first evaluated in both diseases of pheochromocytoma and neuroblastoma globally and secondly in each disease separately. As mentioned in methods section, cytopathology or if not available a composite reference standard (CRS) consisting of biomarkers, imaging, and the six-month follow-up evaluations was considered as the gold standard (positive CRS means the presence of disease and negative CRS means the absence of disease) in this study. The overall results of the study in both diseases showed positive ^{131}I-MIBG study in 47.5%, positive octreotide study in 42.5%, and positive CRS in 47.5% of patients. Comparison of the studies by these two agents revealed higher sensitivity for ^{131}I-MIBG than octreotide, both in patient-based analysis (100% vs. 80.9%, respectively), and lesion-based analysis (94.4% vs. 80.56%, respectively) (Figure 1, Table 1). Diagnostic performance of these two agents in each of pheochromocytoma and neuroblastoma, are shown in Table 2. In pheochromocytoma ^{131}I-MIBG and octreotide are both highly sensitive (100%), while ^{131}I-MIBG is more specific (100% vs. 87.5%).

In neuroblastoma, ^{131}I-MIBG is more sensitive than octreotide (100% vs. 81.25%).

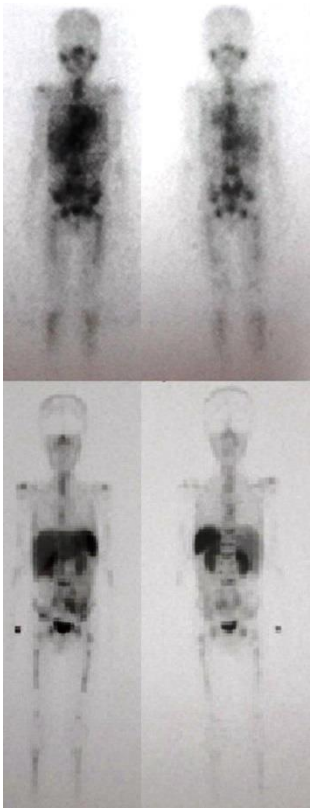

Fig 1. Anterior (left) and posterior (right) Images of a 6 year old patient with neuroblastoma: ^{131}I-MIBG scan shows multiple sites of tumoral involvement in the skeleton (above) and ^{99m}Tc-HYNIC-TOC scan of the patient shows the same findings as ^{131}I-MIBG study, but with better resolution (below).

Table 1: Overall sensitivity and specificity for ^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC scans, analyzed by patient-based and lesion-based data, in neuroendocrine tumors of pheochromocytoma and neuroblastoma.

Scan type	Patient-based		Lesion-based	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
^{131}I-MIBG	100 (95%CI=82.3-100)	95.2 (95%CI=76.2-99.8)	94.4 (95%CI=81.3-99.3)	95.2 (95%CI=76.2-99.8)
^{99m}Tc-HYNIC-TOC	80.9 (95%CI=58.9-94.5)	94.7 (95%CI=74.0-99.9)	80.6 (95%CI=64.0-91.8)	95.8 (95%CI=76.2-99.9)

Table 2: Diagnostic performance of ^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC scans in each of pheochromocytoma and neuroblastoma diseases.

Scan type	Patient-based		Lesion-based	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
^{131}I-MIBG	100 (95%CI=29.2-100)	100 (95%CI=63.1-100)	100 (95%CI=79.4-100)	92.85 (95%CI=66.1-99.8)
^{99m}Tc-HYNIC-TOC	100 (95%CI=29.2-100)	87.50 (95%CI=47.3-99.7)	81.25 (95%CI=54.35-95.9)	100 (95%CI=75.3-100)

Table 3: Sensitivity and specificity of ^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC scans in different parts of the body, analyzed by patient-based and lesion-based data, in neuroendocrine tumors of pheochromocytoma and neuroblastoma.

Lesion site		^{131}I-MIBG		^{99m}Tc-HYNIC-TOC	
		Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)
Patient-based	Head and neck	100 (47.8-100)	100 (90.0-100)	80.0 (28.3-99.4)	100 (90.0-100)
	Thorax	83.3 (35.8-99.3)	100 (89.7-100)	100 (54.0-100)	100 (89.7-100)
	Abdomen	100 (78.2-100)	100 (86.2-100)	80.0 (73.5-100)	96.0 (79.6-99.9)
	Extremity	100 (75.8-100)	97.1 (85.0-99.9)	100 (47.8-100)	97.1 (85.0-99.9)
Lesion-based	Head and neck	87.5 (47.3-99.6)	100 (90.0-100)	75.0 (34.9-96.8)	100 (90.0-100)
	Thorax	60.0 (14.6-94.7)	100 (89.7-100)	80.0 (28.3-99.4)	100 (89.7-100)
	Abdomen	100 (80.4-100)	100 (86.2-100)	70.5 (44.4-89.6)	96.0 (79.6-99.9)
	Extremity	100 (59.0-100)	97.1 (85.0-99.9)	100 (59.0-100)	100 (59.0-100)

Table 4: Intensity of uptake by the lesions in different parts of the body in each of ^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC scans.

Part of the body	Intensity of uptake	^{131}I-MIBG	^{99m}Tc-HYNIC-TOC
Head and neck	Mild	2 (5.0)	2 (5.0)
	Moderate	2 (5.0)	1 (2.5)
	Severe	1 (2.5)	1 (2.5)
	None	35 (87.5)	36 (90.0)
Thorax	Mild	1 (2.5)	1 (2.5)
	Moderate	1 (2.5)	3 (7.5)
	Severe	3 (7.5)	2 (5.0)
	None	35 (87.5)	34 (85.0)
Abdomen	Mild	1 (2.5)	7 (17.5)
	Moderate	2 (5.0)	3 (7.5)
	Severe	12 (30.0)	3 (7.5)
	None	25 (62.5)	27 (67.5)
Extremity	Mild	1 (2.5)	3 (7.5)
	Moderate	3 (7.5)	2 (5.0)
	Severe	1 (2.5)	1 (2.5)
	None	35 (87.5)	34 (85.0)

The data regarding sensitivity and specificity of these two agents in different parts of the body (head and neck, thorax, abdomen, extremities), on the basis of both patient based and lesion-based analyses reveals that ^{131}I-MIBG has a higher sensitivity for detection of lesions in abdominal and head and neck areas while octreotide shows a better sensitivity in thoracic region. In extremities both agents reveal similar sensitivities. Concerning the specificity, although both agents are highly specific in all parts of the body, ^{131}I-MIBG shows higher specificity in abdomen than octreotide scan (Table 3).

Considering the pattern of lesions determined by intensity of uptake (mild, moderate, severe) and distribution/extent of the involvement (single focus, multifocal, widespread), the most intense lesions were detected primarily in abdomen followed by thorax in both studies (Table 4), and unifocal involvement was more frequent in the abdomen (Table 5).

Table 5: Extent of lesions in different parts of the body in each of ^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC scans.

Part of the body	^{131}I-MIBG	^{99m}Tc-HYNIC-TOC
Head and neck	35 (87.5)	36 (90.0)
	1 (2.5)	0 (0.0)
	3 (7.5)	3 (7.5)
	1 (2.5)	1 (2.5)
Thorax	35 (87.5)	34 (85.0)
	3 (7.5)	4 (10.0)
	0 (0.0)	0 (0.0)
	2 (5.0)	2 (5.0)
Abdomen	25 (62.5)	27 (67.5)
	10 (25.0)	9 (22.5)
	3 (7.5)	2 (5.0)
	2 (5.0)	2 (5.0)
Extremity	35 (87.5)	35 (87.5)
	1 (2.5)	1 (2.5)
	3 (7.5)	3 (7.5)
	1 (2.5)	1 (2.5)

DISCUSSION

Pheochromocytoma and neuroblastoma the two most important tumors arising from the adrenal medulla, are evaluated in this study by two radionuclide imaging methods ^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC. Both tumors may also arise from extra-adrenal sites, specifically, in the paraganglia of the sympathetic chain. Pheochromocytoma is characterized by excess catecholamine secretion and sympathomimetic symptoms, which can precipitate life-threatening hypertension or cardiac arrhythmias [13, 14].

In approximately 10% of patients pheochromocytoma is bilateral. When these tumors arise outside of the adrenal gland, they are termed extraadrenal pheochromocytomas, or paragangliomas which are about 10-20% of patients [13]. Pheochromocytomas are increasingly seen with other neuroectodermal hereditary disorders including MEN2, von Hippel-Lindau disease, neurofibromatosis, tuberous sclerosis and Carney syndrome. The diagnosis of pheochromocytoma is suggested by detection of elevated blood or urinary catecholamines, although there are many other causes for these laboratory findings. CT or MRI is often the first imaging modality being used [13-15].

Neuroblastoma is a malignant tumor of neural crest origin, occurring mainly in young children, usually less than 4 years of age. The majority is sporadic (98%), but familial neuroblastoma is reported [16]. Seventy percent of the tumors originate in the retroperitoneal region, either from the adrenal or the abdominal sympathetic chain; however, 20% occur in the chest, deriving from thoracic sympathetic chain. More than 90% of neuroblastomas produce catecholamines [13].

These tumors can be evaluated by two radionuclide imaging agents including radioiodinated MIBG and Tc-99m octreotide, which were used in this study. MIBG is a noradrenaline and guanethidine analog, and is radiolabeled with I-131/I-123 as ^{131}I-MIBG and ^{127}I-MIBG. These agents are used for scintigraphy of tumors with neuroendocrine origin, particularly those of the neuroectodermal (sympathoadrenal) system including pheochromocytoma, paraganglioma and neuroblastoma [17, 18], although other neuroendocrine tumors, such as medullary thyroid carcinoma, carcinoid tumor, merkel cell tumor of the skin, and metastases of these tumors, have been shown to take up MIBG [17, 19]. Sensitivity of this agent for detection of pheochromocytoma is about 90%, with specificity being greater than 95%. For neuroblastoma MIBG sensitivity is greater than 90%, with specificity of 95% [13].

Neuroendocrine tumors (NET) are derived from embryonic neural crest tissue. As the peptides and hormones produced by these cells are found in both the central nervous system and the endocrine system, they are called neuroendocrine tumors. Somatostatin is a hormone that inhibits synthesis of hormones and peptides by neuroendocrine cells, hence is used therapeutically to reduce the release of these agents by the NET, thereby helping to control or reduce tumor growth.

Labeling of a somatostatin analog called octreotide with radioisotopes such as In-111 provided a

diagnostic tool for detection of NETs that expressed somatostatin receptors, namely subtype II and V [20].

Tumors including pheochromocytoma, neuroblastoma, ganglioneuroma and paraganglioma are among tumors with high expression of somatostatin receptors, and can be detected by somatostatin analog imaging (octreotide scintigraphy) [21].

According to the previous studies, ^{131}I-MIBG has high sensitivity and specificity for detection of tumors with adrenal origin such as pheochromocytoma, and also was considered as a selective diagnostic tool for detection of neuroblastoma [3-10, 13]. The specificity of MIBG for detecting primary and secondary neuroblastoma approaches 100%. The sensitivity in detecting sites on a lesion-by-lesion basis is about 80% and the sensitivity in terms of staging is 90-95% [19].

Besides, some studies suggest high diagnostic value of octreotide imaging in detecting NETs. In pheochromocytoma, neuroblastoma, and paraganglioma, sensitivity of In-111 pentetreotide imaging is greater than 85% [21, 22]. Also, it seems that somatostatin receptor scintigraphy can be superior to MIBG concerning more cost-effectiveness, lower radiation dose to the patient, shorter required time for imaging, as well as higher imaging quality [23-25] .The present study hence aimed to assess and compare the diagnostic power of the two procedures of ^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC imaging in diagnosis and localization of pheochromocytoma and neuroblastoma which are the two most frequent types of neuroendocrine tumors. Overall results in both diseases, based on both analysis approaches (patient-based and lesion-based analyses) showed that with regard to sensitivity, ^{131}I-MIBG was superior to ^{99m}Tc-HYNIC-TOC imaging; however the two tools had about similar high specificity (Table 1).

Evaluation of each of two diseases separately, shows that in pheochromocytoma both agents are perfectly sensitive (100%), but ^{131}I-MIBG is more specific than octreotide (100% vs. 87.5%). In neuroblastoma, ^{131}I-MIBG is more sensitive than octreotide (100% vs. 81.25%) (Table 2).

In a study [25], MIBG had higher accuracy than somatostatin analogs in detection of pheochromocytoma, but for other neuroendocrine tumors, imaging by somatostatin analogs were more applicable. Our study regarding pheochromocytoma also ^{131}I-MIBG revealed higher accuracy than ^{99m}Tc-HYNIC-TOC demonstrating of perfect 100% sensitivity and specificity; although ^{99m}Tc-HYNIC-TOC also showed good accuracy. However, two studies have shown superiority of somatostatin receptor scintigraphy (SRS) over MIBG in patients with paraganglioma, especially in the head and neck area [15, 26].

In another study [27], MIBG sensitivity was again higher than somatostatin analog for diagnosing of neuroblastoma, supporting our results. The lower sensitivity of octreotide imaging for detection of these tumors may be attributed to concentration of subtypes of somatostatin receptors. The sensitivity of octreotide imaging is higher when the tumors express more subtype 2 of somatostatin receptor, as other subtypes can also be found in these tumors. From in vitro and in vivo studies, it has been established that somatostatin receptor subtypes 3 and 4 are also expressed in pheochromocytoma, including adrenal and metastatic disease [28]. In-111pentetreotide (Octreoscan; Mallinckrodt Inc.) has only moderate affinity for these subtypes, compared with subtypes 2 and 5, SRS has been used with variable results to detect this tumor [25, 29].

Our data regarding sensitivity and specificity of these two agents in different parts of the body reveals that ^{131}I-MIBG has a higher sensitivity for detection of lesions in abdominal and head and neck areas, while ^{99m}Tc-HYNIC-TOC shows a better sensitivity in thoracic region. This finding indicates additional usefulness of octreotide scan in detection of thoracic lesions not detectable on ^{131}I-MIBG imaging. The reason could be due to physiologic cardiac uptake of MIBG which may interfere with interpretation in the thorax. In a study [30], it was indicated that octreotide can be helpful to detect tumor lesions if MIBG studies were negative. Limouris et al [29] also asserted that octreotide imaging is of value in cases with negative MIBG results, but MIBG could not be completely replaced with octreotide. In extremities both agents reveal similar sensitivities in our study. Concerning the specificity, although both agents are highly specific in all parts of the body, ^{131}I-MIBG shows higher specificity in abdomen than ^{99m}Tc-HYNIC-TOC scan. This finding could be attributed bowel activity in octreotide scintigraphy causing more false positive results in our study.

In assessment of lesion intensity, we found that in most sites especially abdomen, the intensity was higher in MIBG than octreotide scanning, as confirmed in another study [25].

A limitation of our study was using I-131 instead of I-123 labeled MIBG, because at the time of the study only I-131 was available for labeling purposes. The most important advantage of ^{123}I-MIBG over I-131 is the possibility of performing single photon emission tomography (SPECT) causing higher sensitivity of 83%-100% and specificity of 95%-100% for detecting pheochromocytoma as described in previous studies [31-33]. Also scintigraphy with ^{123}I-MIBG, compared with ^{131}I-MIBG, is advantageous because of its optimal γ-emissions and lack of ß-particles that result in a lower absorbed dose [13]. In addition, the I-123 isotope not only gives rise to better quality planar

images, it provides required high photon flux for favorable SPECT imaging, increasing the diagnostic accuracy [13,17].

CONCLUSION

Overall, our findings indicate that ^{131}I-MIBG is slightly superior over ^{99m}Tc-HYNIC-TOC scanning in detection of both neuroblastoma and pheochromocytoma tumors. However, a combination of these two diagnostic scintigraphies can provide more complete information on the nature and the site of the lesions, especially in the thoracic region. Also, in cases with octreotide avid lesions, follow-up studies can be preferable using this agent, with less radiation burden. Each study can be replaceable if one proved to be negative.

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