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“Operating on Shadows”: Evolving Perceptions of the Incidentally Discovered Adrenal Mass, 1982-2002

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Abstract

Computed tomography (CT) scanning is an integral component of 21st-Century medical practice, and physicians have become increasingly reliant on this imaging modality for diagnosing disease and planning operative treatment. Following its introduction in the 1970s, CT scanning proved especially valuable for studying the organs of the abdominal cavity. However, with the rapid rise in the number of abdominal CT scans came an unanticipated problem: the identification of clinically silent adrenal tumors of unknown significance. The recognition of these asymptomatic, incidentally discovered adrenal tumors, dubbed “incidentalomas” by George Washington University surgeon Glenn Geelhoed in 1982, compelled physicians to embark on extensive hormonal workups, order further radiographic studies, and, in many cases, perform operations of questionable benefit.

In this paper I provide a historical analysis of adrenal incidentaloma from its initial recognition in 1982 until the National Institutes of Health-mandated consensus conference dedicated solely to its management in 2002. First, I explore the circumstances and historical context surrounding the early reports of adrenal incidentaloma, and describe how this entity received its name. Next, I trace the efforts of three separate classes of physicians (endocrinologists, radiologists, and surgeons) to characterize these tumors and formulate rational guidelines for their treatment. Finally, I reflect upon the impact that adrenal incidentaloma has made upon medical thought and practice during its relatively short existence. Throughout this paper I show how adrenal incidentaloma has transformed the traditional diagnostic algorithms of adrenal disease, altered definitions of illness and wellness in subtle but significant ways, and forced physicians to come to terms with uncertainty in a practice environment that increasingly expects them to provide unassailable, error-free care.

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Introduction

On February 4, 2002, the National Institutes of Health (NIH) hosted an unusual "state of the science" conference at its headquarters in Bethesda, Maryland.[1] Instead of targeting a specific disease, therapy, or patient population, this conference was dedicated to a radiographic finding. The subject of the two-and-a-half day meeting was the "clinically inapparent adrenal mass," otherwise known as adrenal "incidentaloma." A panel of 12 experts was charged with providing consensus guidelines for the management of incidentally discovered adrenal tumors, to be made immediately available to physicians, journalists and the public on the NIH website following the meeting.[2] The 12 experts represented a variety of fields, including endocrinology, radiology, surgery, pathology, epidemiology, and oncology; one member was a non-physician from a patient advocacy group. An additional 21 invited speakers from the U.S. and abroad gave a series of talks on the current state of knowledge, practice, and opinion regarding adrenal incidentaloma. After listening to the assembled speakers and wading through the existing literature on the subject over the course of a day and a half, the panel gathered to discuss their findings and record their recommendations. The deliberations carried on into the early hours of the next morning, but later that day the NIH would release a 26-page summary statement detailing the panel's findings and providing practitioners and patients with a framework of information based on the best evidence available at the time. The

[1] National Institutes of Health, Program and Abstracts from the NIH State-of the Science Conference on the Management of the Clinically Inapparent Adrenal Mass ("Incidentaloma"), February 4-6, 2002 (Bethesda, NIH, 2002): 3.
[2] National Institutes of Health, 9-10.

head of the consensus panel, Dr. Melvin Grumbach, Professor of Pediatrics at the University of California, San Francisco (UCSF), would later describe his experience at the conference as “jury duty in a scientific court.”[3]

Radiography is an integral component of modern medical practice, and within the past few decades physicians have witnessed a tremendous increase in the number of imaging modalities available as well as the overall accuracy of the studies being performed. With the existing armamentarium of X-rays, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), angiography, nuclear medicine, and numerous other modalities in use or in development, there exist few, if any, areas of the human body that are not accessible or visible to the radiologist. The rise of radiographic technology has been accompanied, however, by a rapid increase in the number of incidentally discovered tumors detected on imaging studies being performed for other clinical indications. The majority of these incidentally discovered tumors, dubbed “incidentalomas” in 1982 by George Washington University surgeon Glenn Geelhoed, are found in otherwise asymptomatic patients.[4] Incidentalomas can be identified in a multitude of organs, but one of the most common sites for these tumors is the adrenal gland. Between 1 and 5% of abdominal CT scans will identify a clinically silent tumor of the adrenal gland.[5] The question of what to do when an adrenal incidentaloma has been discovered is a source of confusion and concern for clinicians and patients alike; the next steps invariably involve the ordering of multiple

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[3] Melvin Grumbach, interview with author, San Francisco, CA, 16 March 2009.
[4] G. W. Geelhoed and E. M. Druy, "Management of the Adrenal 'Incidentaloma'," Surgery 92.5 (1982): 866.
[5] W. F. Young, Jr., "Clinical Practice: The Incidentally Discovered Adrenal Mass," N Engl J Med 356.6 (2007): 601.

biochemical tests and additional radiographic studies, and in some cases surgery is required for a definitive answer. As a result, thousands of asymptomatic people each year undergo extensive diagnostic testing and possible surgery for an entity of uncertain clinical significance. Heightened patient anxiety is an understandable by-product of this process. With the ongoing reliance on imaging studies by clinicians, the continually increasing aging population, and the widespread use of whole-body CT scans for health care "screening" by the public, the number of adrenal incidentalomas identified each year will continue to grow, levying an enormous cost to the U.S. health care system.

In this paper I examine the historical background for the modern clinical entity of adrenal incidentaloma. Radiologists have commented on asymptomatic adrenal masses since the first X-ray images of the adrenal gland in the mid-20th Century, but it was not until the introduction of CT scanning in the 1970s that adrenal incidentaloma became recognized as an unintended consequence of radiography and a potentially large-scale problem for clinicians. The first published reports of incidentally discovered adrenal tumors were from the early 1980s; in the first chapter of this paper I analyze two of these early reports and show how they raised questions that would persist throughout the subsequent decades regarding the clinical significance and appropriate management of these tumors. The authors of these papers recognized even at this early stage that adrenal incidentalomas required clinicians to alter their traditional algorithms for diagnosing and treating adrenal disease, and thus generated uncertainty and anxiety regarding the decision to treat or observe them. I pay special attention to

the 1982 paper by Geelhoed, in which he was the first to use the word “incidentaloma” to describe an incidentally discovered adrenal mass; the origins of this new word, which has become an accepted part of medical terminology, shed light on the environment of confusion and uncertainty from which it was born.

Following Geelhoed’s 1982 paper, physicians from a variety of specialties recorded their own experiences with adrenal incidentaloma and provided the first management guidelines based upon the limited experience available at the time. In the second chapter of this paper I explore the efforts of endocrinologists to characterize the hormonal profiles of adrenal incidentalomas. Endocrinologists refined the use of hormonal testing to determine biochemical function of adrenal incidentalomas, and identified a new class of previously unrecognized patients with “subclinical” hormone secretion who could potentially benefit from earlier treatment. The process of uncovering these new syndromes of subclinical hormone secretion forced physicians to revise their perceptions of “symptomatic” and “asymptomatic” adrenal disease; in essence, the definitions of what constituted a “typical” patient with adrenal disease were completely altered. In addition, the discovery of subclinical hormone secretion syndromes changed the expectations of what surgery for adrenal disease could “fix;” patients who were previously thought to be “healthy” were shown to “improve” clinically following operations for subclinical hormone secretion, thereby prompting increasing numbers of physicians to recommend operation for patients with adrenal incidentalomas and even borderline hormone “activity”. However, since no one

knew the true natural history of these newly identified subclinical hormone secretion syndromes, the discovery of these new phenomena raised broader questions about how physicians should best balance the potential benefits of identifying and treating adrenal disease at an early stage with the risks of over-diagnosing an asymptomatic population with low overall risk for adrenal disease and exposing them to the risks of testing and treatment unnecessarily.

While endocrinologists were charged with establishing the hormonal profiles of adrenal incidentalomas, radiologists and surgeons sought to predict the risk of malignancy in these tumors. The third chapter of this paper focuses on the often difficult process of determining the malignant potential of adrenal incidentaloma in the decades following its initial discovery. Radiologists established standardized measurements of tumor density as measured in Hounsfield units; this system improved the understanding of malignancy risk in adrenal incidentaloma, and also served to improve communication between the various types of physicians dealing with these tumors. However, the use of Hounsfield units to determine malignancy was also shown to have significant limitations, which underscored the difficulties that physicians faced in attempting to use “black and white” quantitative data to characterize the decidedly “grey” entity of adrenal incidentaloma. The other radiographic feature that was utilized as a predictor of malignancy during this period was tumor size; surgeons offered a variety of tumor size cutoffs as absolute indications for operation, and their opinions on these criteria closely mirrored their willingness to deal with the uncertainty engendered by these clinically silent adrenal tumors. In the midst of

this rapidly evolving field of understanding of adrenal incidentalomas emerged the new technique of laparoscopic adrenalectomy, which provided surgeons with a minimally invasive, less morbid means through which to remove adrenal tumors. The introduction of laparoscopic adrenalectomy in 1992 further changed the perceptions of physicians regarding the management of adrenal incidentalomas; now that the act of removing an adrenal tumor had been transformed into a relatively low-risk endeavor, a dramatically increased number of patients with adrenal incidentalomas underwent operation in the subsequent decade. However, several factors in addition to the new technology of laparoscopic adrenalectomy had contributed to this rapid rise in the number of adrenal operations, and highlighted just how far the scales had tipped in favor of intervention versus observation in the short time since the initial recognition of adrenal incidentaloma.

The final section of this paper revisits the 2002 NIH conference on the "clinically inapparent adrenal mass" and then provides some reflections on the impact of this "disease of modern technology."[6] I review the areas of controversy surrounding adrenal incidentaloma and how the panel achieved consensus regarding a broad range of topics in the short span of two and a half days. Recent developments in adrenal imaging, hormonal testing, and minimally invasive surgery had a profound influence on the panel's recommendations and were evidence of the tremendous amount of research that had been performed on an entity that had been recognized just 2 decades earlier. Nevertheless, many

[6] R. M. Chidiac and D. C. Aron, "Incidentalomas: A Disease of Modern Technology," Endocrinol Metab Clin North Am 26.1 (1997): 233.

questions remained, and the panel challenged researchers the world over to improve the knowledge and management of adrenal incidentaloma.

Through my historical analysis of adrenal incidentaloma, I aim to demonstrate how this clinical entity represents an unintended consequence of modern imaging technology, and how the recognition and investigation of these adrenal tumors presaged the efforts of current physicians to understand the bewildering assortment of incidentalomas of other organs throughout the body. In addition, I explore how the seemingly innocuous radiographic finding of a clinically silent adrenal tumor has created new definitions of illness and wellness for both physicians and patients and has altered some of the traditional algorithms of medical practice, as well as the expectations of what physicians are able to diagnose and treat. Finally, I utilize the story of adrenal incidentaloma as a means to investigate the broader question of how physicians deal with uncertainty in the modern environment of medical practice, where they are barraged by a constant stream of information regarding patients' health through laboratory testing, radiography, genetic screening, and a panoply of other diagnostic measures.

Chapter 1: The Discovery and Naming of Adrenal "Incidentaloma"

The adrenal glands are two triangular structures that normally measure 1 centimeter or less and are located on top of the kidneys, posterior to the abdominal cavity. The Italian anatomist Bartolomeo Eustachi provided the first anatomic descriptions of the adrenal glands in the 16th Century, but the multiple hormonal functions of the adrenals were not delineated for another 300 years.[7] The adrenal glands are composed of two separate tissue types with differing embryologic origins: the cortex and medulla. Hormones secreted by the adrenal cortex help to regulate the body's salt and water levels, glucose metabolism, and sex hormone production. The adrenal medulla secretes hormones to control the body's response to stress. Tumors of the adrenal gland are found in approximately 3% of the population over 50 years of age in autopsy studies.[8] The majority of these adrenal tumors are neither malignant nor hormonally active, and are clinically silent. Functioning tumors of the adrenal gland are less commonly identified, and may be associated with clinically significant symptoms and signs such as hypertension, derangements of blood glucose and electrolytes, changes in body habitus, and psychological impairment. Tumors of the adrenal medulla that secrete excess catecholamines (pheochromocytoma) can cause life-threatening hypertensive crisis, cardiovascular collapse, and stroke. The adrenal gland may be a site of metastases from cancers of other organs, including lung,

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[7] R. B. Welbourn, The History of Endocrine Surgery (New York: Praeger, 1990): 147.
[8] G. Mansmann, J. Lau, E. Balk, M. Rothberg, Y. Miyachi and S. R. Bornstein, "The Clinically Inapparent Adrenal Mass: Update in Diagnosis and Management," Endocr Rev 25.2 (2004): 310.

breast, kidney, and melanoma. Primary adrenal cancers are exceedingly uncommon, with 1-2 cases per million people in the U.S. diagnosed each year.[9]

Because the normal adrenal glands are small, surrounded by retroperitoneal fat, and in close proximity to other larger organs such as the liver, spleen, and pancreas, early radiographs did not typically identify them. Adrenal glands cannot be seen on plain X-rays unless they are calcified or quite enlarged. More advanced imaging techniques introduced in the mid-20th Century gave radiologists slightly improved views of the adrenal glands; these techniques included excretory urography, contrast angiography, radioisotope scanning and ultrasound.[10] However, these modalities were still inadequate for identifying normal adrenal glands and most small adrenal tumors, and were dependent on the amount of contrast material administered, timing of the study, and experience level of the person performing and interpreting the study. In many instances the image of the adrenal gland obtained by these modalities offered only a suggestion or shadow of where the gland might reside. Radiologists during this period would occasionally comment on the “accidental” finding of an adrenal mass during abdominal imaging, but these were rare occurrences that did not appear to merit much attention from radiologists or other physicians.[11] Prior to the 1970s, adrenal tumors were not diagnosed until they secreted enough hormones to generate signs and symptoms of hormonal excess, or grew large

[9] W. T. Shen, C. Sturgeon and Q. Y. Duh, "From Incidentaloma to Adrenocortical Carcinoma: The Surgical Management of Adrenal Tumors," J Surg Oncol 89.3 (2005): 190.
[10] Ernest J. Ferris and Joanna J. Seibert, Urinary Tract and Adrenal Glands: Multiple Imaging Procedures (New York: Grune & Stratton, 1980): 473.
[11] Leo G. Rigler, Outline of Roentgen Diagnosis, 2d ed. (Philadelphia: J. B. Lippincott company, 1943): 721.

enough to become palpable on physical examination or cause discomfort to the patient. A 1974 paper by Bernard Lewinsky from the Royal Marsden Hospital in London detailed the clinical presentation of 178 patients with non-functioning adrenal tumors; nearly all of the patients exhibited a palpable mass or abdominal pain that prompted diagnostic evaluation and treatment, and none of the patients was asymptomatic.[12]

The imaging modality that gave radiologists the first clear pictures of the adrenal glands was computed tomography (CT). Invented over the course of the 1960s and early 1970s through separate efforts by Allan Cormack of South Africa and Godfrey Hounsfield of England (who were later awarded a joint Nobel Prize in Medicine in 1979), the CT scanner uses X-rays to generate thin cross-sectional images that can be formatted to create a three-dimensional reconstruction of the body.[13] The first commercially available CT scanners were introduced between 1974 and 1976 and shortly thereafter radiologists began utilizing this technology for identifying normal and diseased adrenal glands. Nolan Karstaedt and colleagues of Washington University in St. Louis published a paper in 1978 describing their initial experiences with CT scanning of the adrenal gland.[14] They first examined 200 “nonpathologic” abdominal scans in order to determine how accurate the technique was in identifying normal adrenal glands. Using different intervals between CT scan “slices,” they were able to

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[12] B. S. Lewinsky, K. M. Grigor, T. Symington and A. M. Neville, "The Clinical and Pathologic Features Of 'Non-Hormonal' Adrenocortical Tumors: Report of Twenty New Cases and Review of the Literature," Cancer 33.3 (1974): 778.
[13] Bettyann Kevles, Naked to the Bone : Medical Imaging in the Twentieth Century, The Sloan Technology Series. (New Brunswick, N.J.: Rutgers University Press, 1997): 145.
[14] N. Karstaedt, S. S. Sagel, R. J. Stanley, G. L. Melson and R. G. Levitt, "Computed Tomography of the Adrenal Gland," Radiology 129.3 (1978): 723.

identify 95% of normal adrenal glands, a tremendous improvement over the less than 50% using prior modalities. This group then performed CT scanning in 29 additional patients with known adrenal tumors and were able to identify all of these tumors, some measuring 1 centimeter or smaller. While the authors stated that CT scanning could demonstrate normal and enlarged adrenal glands "safely, rapidly, and effectively," they urged caution in drawing "definite conclusions" about "specific pathologic diagnosis" from the results of CT scans and deferred to their colleagues in endocrinology to provide definitive identification of adrenal tumors based on biochemical tests and other non-radiographic information.[15] At this early stage in the history of CT scanning, patients undergoing adrenal imaging were still expected to present with "clinical and/or biochemical evidence of disturbance in adrenal function" or "palpable upper-abdominal mass;" CT scan was used to confirm the clinical diagnosis and to replace other more invasive radiographic methods. The authors did mention the possibility of identifying incidental adrenal enlargement or "previously silent metastatic disease" on CT scan during "investigation of another suspected abnormality," but focused almost all of their attention on clinically detectable adrenal masses.[16] Within a few years, the typical algorithms for the workup of adrenal disease would be dramatically changed, and CT scan would become the primary means by which adrenal disease was diagnosed. As the number of abdominal CT scans and the experience of the radiologists interpreting them increased, physicians soon

[15] Karstaedt, 728.
[16] Karstaedt, 728.

began to notice a parallel increase in the number of incidentally discovered adrenal masses.

Richard Prinz, a surgeon at the Loyola University School of Medicine in Chicago, reported in 1982 on his institution's experience with nine asymptomatic patients who had incidentally discovered adrenal masses found on abdominal CT scan.[17] Published in the Journal of the American Medical Association, this was the one of the first papers to specifically investigate the problem of incidental adrenal mass found on CT scan. The nine patients described in the paper did not manifest any of the traditional signs and symptoms of adrenal hormone excess, although eight of the nine had hypertension (as will be explored in the next chapter, one might argue that these patients were not truly "asymptomatic"). The tumors detected on CT scan ranged in size from 1 to 4 centimeters, representing minimal to modest increase in size from normal. All patients underwent biochemical testing for hormone excess, but only one had definitively elevated catecholamines (pheochromocytoma), a clear indication for operation. Because of the uncertain risk of malignancy, seven of the remaining eight patients were taken to the operating room for open adrenalectomy, which is a major abdominal operation requiring several days of hospitalization and significant postoperative pain. The final pathology results of the tumors removed included four benign cortical adenomas, two benign cysts, one lipoma (benign fatty tumor), and one pheochromocytoma (which had been suspected preoperatively by biochemical tests). There were therefore no cancers found in any of the operative specimens.

[17] R. A. Prinz, M. H. Brooks, R. Churchill, J. L. Graner, A. M. Lawrence, E. Paloyan and M. Sparagana, "Incidental Asymptomatic Adrenal Masses Detected by Computed Tomographic Scanning: Is Operation Required?," JAMA 248.6 (1982): 701.

The subheading of Prinz's paper asked "Is Operation Required?": in retrospect, only one of the eight patients who underwent adrenalectomy actually benefited from surgery. Because of this low rate of hypersecreting or malignant tumors, Prinz urged that "care in interpreting the clinical significance of these masses and caution in recommending treatment are required."[18] Even at this early stage of recognition of these incidental adrenal tumors, Prinz was able to pinpoint the major source of tension that they raised:

> "Does detection of these anatomic abnormalities offer hope for early diagnosis and treatment of adrenal neoplasms so that complications of hormone-producing neoplasms can be lessened and the dismal prognosis of malignant tumors can be improved? Or does CT merely bring to clinical attention adrenal enlargements that do not pose a threat to the patient's overall health?"[19]

Prinz therefore recommended hormonal testing on all patients with incidentally discovered adrenal masses, along with a careful search for primary cancers in other organs that could metastasize to the adrenal gland. If these inquiries turned up no positive information, then he believed that "treatment must be individualized,"[20] and offered a possible tumor size cutoff of 3 centimeters, or any growth on serial examinations as possibly indicating increased risk of cancer. These guidelines would be refined and built upon by numerous other clinicians in subsequent years. In this influential 1982 article, Prinz thus alerted the medical community to the new clinical entity of the incidentally discovered adrenal mass, and framed the question of how these tumors should be perceived by clinicians: as harbingers of future malignancy or hormonal hyperactivity that merited aggressive treatment, or as inconsequential radiographic findings that could be

[18] Prinz, 703.
[19] Prinz, 703.
[20] Prinz, 704.

left alone? The incidentally discovered adrenal mass would soon receive a catchier name, one that played upon the uncertainty and confusion that it generated.

Glenn Geelhoed was a staff surgeon at the George Washington University Hospital in Washington, D.C. with a special interest in tumors of the endocrine organs. On April 5, 1982, he presented a paper at the Third Annual Meeting of the American Association of Endocrine Surgeons in Houston, Texas in which he described his experience with the management of 20 incidentally discovered adrenal tumors.[21] The resultant paper, co-authored with radiologist Edward Druy, was published in Surgery later that year, a few months after Prinz's paper in JAMA. In his presentation Geelhoed highlighted the fact that in previous decades, patients with adrenal tumors almost always presented with signs and symptoms of hormonal excess, and that "the inability of localization techniques to reveal the anatomic source of functional abnormalities" was the major limiting step in treating the problem.[22] The invention of abdominal CT scanning, however, had created an "obverse problem": the "discovery of masses of unknown or doubtful clinical significance."[23] CT scan had become the point of diagnosis rather than the confirmation of clinical suspicion or positive lab tests for these patients. Geelhoed went on to present 20 patients with incidentally discovered adrenal masses, most of which were discovered on abdominal CT scanning. He detailed the clinical presentations of the patients, the radiographic appearances of the tumors, and the subsequent hormonal testing that was performed. Only

[21] Geelhoed, 866.
[22] Geelhoed, 866.
[23] Geelhoed, 866.

one patient had biochemical abnormalities, and these results were equivocal at best. Nine patients ultimately underwent open adrenalectomy, almost "solely on the basis of the abnormal adrenal images."[24] Of these nine patients, six had benign pathology, mostly cysts or cortical adenomas; one of these patients had a completely normal adrenal gland. The remaining three patients included two with adrenal metastases from lung cancer, and one with an incorrect diagnosis who actually had a large retroperitoneal sarcoma that did not originate from the adrenal gland. Thus, no cases of hormone-secreting tumors and no cases of primary adrenal malignancy were identified from these 20 patients with incidentally discovered adrenal masses. Geelhoed stated that the radiographic findings of incidental adrenal tumors in these patients therefore "proved unnecessary and even harmful information in many of these patients."[25]

Geelhoed was not shy in stating his opinions regarding the potential hazards with identifying these clinically silent adrenal tumors. He urged caution in interpreting the information provided by radiographs in the absence of solid clinical evidence; otherwise surgeons would merely be "operating on shadows."[26] Since "the adrenal gland is no longer as hidden as it once was,"[27] clinicians would soon be facing increasing numbers of these incidental adrenal masses, and would need to remember that "the presence of an adrenal mass is not an indication for its removal."[28] As proven by Geelhoed's own experience of taking out multiple benign lesions with no primary adrenal cancers or hormonally active

[24] Geelhoed, 867.
[25] Geelhoed, 867.
[26] Geelhoed, 871.
[27] Geelhoed, 872.
[28] Geelhoed, 872.

tumors to show for it, surgeons were in danger of subjecting patients to invasive operations with no clear benefit. Geelhoed was thus in a somewhat unusual position for a surgeon; rather than recommending intervention, he was serving as a self-proclaimed "protector of the adrenal gland"[29] against both unnecessary surgery as well as "the promiscuous use of adrenal imaging."[30] Echoing some of the themes raised in Prinz's JAMA paper from earlier in the same year, Geelhoed's paper brought to light a few of the most salient problems created by incidental adrenal tumors: the reversal of the conventional algorithms for diagnosis of adrenal tumors, the predilection of clinicians to seek action rather than inaction when faced with situations of uncertainty, and the rise to dominance of radiographic technology over clinical judgment.

Besides being one of the earliest case series of patients with incidentally discovered adrenal tumors, Geelhoed's 1982 paper continues to be widely cited today because it was the first published usage of the term "incidentaloma." Geelhoed did not explicitly define the term in his paper but did use it to describe any asymptomatic adrenal mass discovered on imaging studies ordered for another indication. The suffix "-oma" is of Greek origin and is used to denote a form of swelling or tumor. Numerous types of benign and malignant growths have names ending in "-oma," including carcinoma, lymphoma, sarcoma, and melanoma. Medical slang includes a few instances where "-oma" is added to an existing word to create a new entity: a "fascinoma" is a fascinating case or patient, a "horrendoma" is an unusually bad or gruesome case or patient.

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[29] Glenn Geelhoed, telephone interview with author, 16 June 2008.
[30] Geelhoed, 872.

Geelhoed coined the term “incidentaloma” to describe an incidentally discovered adrenal tumor, and after the 1982 publication of this initial paper, the name stuck. Geelhoed now states that his initial creation of the word “incidentaloma” was intended to be sarcastic; by creating a somewhat funny name he was “belittling the diagnosis” and drawing attention to the fact that the majority of these tumors were not of any clinical importance.[31] In the paper he stated repeatedly that adrenal incidentalomas represented a “non-disease”[32] in the majority of cases, and that rational clinical decision-making should always trump a radiographic finding of unknown significance. Despite Geelhoed’s intentions to use levity to help defuse some of the anxiety that these tumors would inevitably evoke in physicians and patients, the word “incidentaloma” would soon become an accepted term in standard medical practice, and its use would be expanded to include incidentally discovered masses in any organ. As Geelhoed now puts it, his simple turn of phrase “turned around to bite me in the butt.”[33]

In the decade that followed Geelhoed’s 1982 Surgery paper containing the first documented use of the word “incidentaloma,” numerous papers on the subject of incidentally discovered adrenal masses were published. Most utilized or made reference to the newly coined term “incidentaloma;” Geelhoed’s half-joking play on words had quickly become part of accepted medical jargon. Interestingly, several of these early papers using the word “incidentaloma” appeared in foreign language journals from both Europe and Asia, a sign that this subject was not just being encountered and analyzed in the U.S., and also an

[31] Geelhoed, interview with author.
[32] Geelhoed, 873.
[33] Geelhoed, interview with author.

indication of the rapid transmission of medical information and terminology in the late 20th Century. The word “incidentaloma” was also applied to incidentally discovered masses in organs other than the adrenal gland, including the pituitary gland, liver, and thyroid. In a 1989 letter to the editors of Surgery, Greek surgeon Dimitrios Linos criticized the rapidly growing usage of the word “incidentaloma”;[34] Linos believed the name to be an inaccurate reflection of the tumor it was meant to describe, and felt that the original meaning behind the name was already being lost, as “incidentaloma” was being used to denote all types of adrenal tumors and not just those incidentally found in otherwise asymptomatic patients. While the name “incidentaloma” was admittedly “euphonic,”[35] Linos proposed that it be replaced by the more precise term “adrenaloma,” which designated the organ of origin and highlighted the difficulty in determining whether the mass was benign or malignant. Linos’ suggested name change never achieved widespread use (except by Linos himself, who published three more papers utilizing his preferred name); Geelhoed’s original term, published in the same journal seven years prior, had already become ingrained in the medical vocabulary.

Abdominal CT scanning was introduced in the mid 1970s, and in less than a decade a new clinical entity borne from this technology had been recognized and named. Prinz and Geelhoed, the first to publish articles on incidentally discovered adrenal masses, were quick to identify the potential problems that these tumors raised. Already, they had demonstrated that adrenal incidentalomas represented a departure from the traditional algorithms of

[34] D. A. Linos, "Adrenaloma: A Better Term Than Incidentaloma," Surgery 105.3 (1989): 456.
[35] Linos, 456.

diagnosis and treatment of adrenal disease, and had warned against the temptation to rush to operation for these tumors, given their exceedingly low overall rate of malignancy. In the years that followed, awareness of adrenal incidentaloma would spread throughout the medical community. A deluge of laboratory tests, further radiographic studies, and operations would follow.

Chapter 2: Uncovering New Syndromes of Subclinical Hormone Secretion During the Evaluation of Adrenal Incidentaloma

Once the clinical entity of adrenal incidentaloma had been recognized and named, physicians were faced with the problem of how to best diagnose and treat patients with these radiographic findings. The two main objectives for diagnosis had been outlined in the earliest papers on the subject by Richard Prinz and Glenn Geelhoed: to rule out hormonal hypersecretion and malignancy. The primary decision related to treatment could be boiled down to a simple question: should the patient have the tumor removed or not? The burden of determining whether an adrenal incidentaloma exhibited hormonal hypersecretion fell primarily on endocrinologists, who had prior expertise in managing patients with clinically overt adrenal diseases. This chapter explores the efforts of endocrinologists to evaluate the hormonal profiles of patients with adrenal incidentalomas during the time period after its initial recognition. Applying the same biochemical tests that they used for patients with obvious clinical signs and symptoms of adrenal hypersecretion, endocrinologists soon uncovered a new class of patients with clinically silent hormonal abnormalities. The discovery of subclinical hormone secretion in patients with adrenal incidentalomas added further uncertainty to an already confusing situation, as clinicians debated whether or not these patients with unexpected radiographic and biochemical findings should be treated. However, it also highlighted the potential benefits of early detection of clinically silent adrenal disease, and was perhaps the best

representation of how adrenal incidentaloma forced clinicians to alter their perceptions of what it meant to have adrenal disease.

Endocrinologists in the early 1980s were presented with a growing population of patients with radiographically identified adrenal masses and no overt signs of hormone hypersecretion. In almost all cases the patient would undergo the same biochemical tests that were utilized for patients with clinically apparent adrenal disease; however, the purpose of testing was different for a subtle but significant reason: rather than using a targeted biochemical test to confirm a strong clinical suspicion in a patient with signs and symptoms of a specific adrenal disease, endocrinologists were applying multiple tests at once in a otherwise healthy patient with the aim of uncovering a hidden diagnosis. Instead of ordering a test with the expectation that it would be positive in the face of other clinical evidence of disease, biochemical testing of adrenal incidentaloma was ordered with the expectation that it would yield negative results, and any positive results were considered surprising. This change in the usual sequence of diagnostic evaluation required endocrinologists to devise new algorithms for hormonal testing in patients with adrenal incidentaloma, and to revise their expectations for what hormonal testing was intended to achieve.

Paul Copeland of the Massachusetts General Hospital published one of the first sets of guidelines for workup of the adrenal incidentaloma in a 1983 article in Annals of Internal Medicine (of note, this same article was selected for republication in Annals of Surgery, one of the most widely read surgical

journals).[36] Copeland made quick reference in his introduction to the uncertainty associated with incidentally discovered adrenal masses, and stated that one of the clinician's objectives was to prevent overtreatment of these tumors, since the majority of them would be nonfunctioning and benign: "if we do not manage these masses appropriately, we may create an iatrogenic disease of medical progress."[37] The goals of workup, therefore, seemed to be less about establishing diagnoses than ruling them out. The evaluation process that he recommended began with a thorough history and physical examination focusing on the manifestations of hormonal excess, then proceeded with biochemical evaluation for the hormones that were most likely to be hypersecreted by an adrenal tumor; specifically, Copeland advocated testing for glucocorticoids (Cushing's adenoma) and catecholamines (pheochromocytoma) in all patients with incidentaloma, and testing for aldosterone (Conn's syndrome) and sex hormones (virilizing or feminizing tumors) in patients with suspicious clinical features detected during focused history and physical examination. Copeland did not provide specific cutoff levels for determining biochemical hypersecretion; he left it to the clinician's judgment whether the results of biochemical testing indicated that the adrenal tumor was "hormonally active and likely to produce detrimental symptoms."[38] The final algorithm that he provided was the first of its kind to be widely utilized by clinicians for the evaluation of adrenal incidentaloma. The algorithm highlighted the importance of tumor size in determining which patients should undergo operation (an issue that will be explored in the following

[36] P. M. Copeland, "The Incidentally Discovered Adrenal Mass," Ann Intern Med 98.6 (1983): 940.
[37] Copeland, 940.
[38] Copeland, 940.

chapter) and was relatively simple in its assessment of hormonal function: tumors were classified as either “active” or “inactive.”[39] Throughout his paper Copeland strongly emphasized the fact that adrenal incidentalomas were extremely unlikely to harbor malignancy or secrete hormones, and even wrote in his final sentence that his algorithm would hopefully “prevent a substantial number of unnecessary operations.”[40] However, clinicians who applied the biochemical tests recommended by algorithms such as Copeland’s would soon uncover a new population of patients with “active” but clinically silent adrenal disease, thereby increasing the overall number of operations being performed and adding to the cloud of uncertainty surrounding adrenal incidentaloma.

Endocrinologists performed biochemical evaluation of patients with adrenal incidentalomas with the aim of ruling out hormonal hypersecretion, but were soon faced with the problem of deciding what to do when one of the tests came back positive in an otherwise asymptomatic patient; they were expected to make “black and white” decisions about how to manage these tumors, but found that many patients fell into a heretofore unrecognized “grey zone.” As more and more patients with adrenal incidentaloma were found to have elevated hormone levels despite not exhibiting any outward manifestations of hormone excess, a new type of diagnosis was established, that of subclinical hormone secretion. The responses of physicians to this newly identified class of patients raised questions regarding the benefits and dangers of early (or “pre-“) diagnosis of adrenal disease. Among the first patients with adrenal incidentaloma to be

[39] Copeland, 944.
[40] Copeland, 945.

identified with subclinical hormone elevations were those with elevated cortisol levels and no apparent sequelae of cortisol excess (Cushing's syndrome). Bernard Charbonnel, an endocrinologist in Nantes, France published one of the first reports of subclinical Cushing's syndrome in 1981.[41] Interestingly, the incidentally discovered adrenal mass in this case report was not identified on abdominal CT scan but was found instead during intravenous urography for the workup of a testicular condition. Further imaging with CT scan, ultrasound, and radioisotope scintigraphy confirmed the presence of the adrenal mass, and biochemical testing revealed a mild elevation in cortisol secretion and abnormal response to suppression testing with dexamethasone, a synthetic steroid analogue. The patient was an otherwise healthy 50-year old man and exhibited none of the characteristic changes in skin or body habitus, or any of the other typical manifestations of Cushing's syndrome. For reasons not provided in the paper, the patient did not undergo adrenalectomy for five years after the diagnosis of adrenal mass, and during this time he did not develop any symptoms of cortisol excess or changes in his biochemical tests. Following operation, however, the patient's cortisol level returned to normal and his responses to dexamethasone testing became normal as well. The authors named this patient's condition "pre-Cushing's syndrome" and wondered whether this case represented a fortuitous early diagnosis ("are all Cushing's adenomas preceded by this situation for a while?"[42]) or a non-morbid, clinically insignificant diagnosis for the patient if left untreated. The fact that no clinical or biochemical

[41] B. Charbonnel, J. F. Chatal and P. Ozanne, "Does the Corticoadrenal Adenoma With 'Pre-Cushing's Syndrome' Exist?," J Nucl Med 22.12 (1981): 1059.
[42] Charbonnel, 1061.

changes occurred during the five years without treatment would point to the latter, but it was impossible to predict whether the patient would have ultimately suffered the metabolic consequences of Cushing's syndrome.

Charbonnel's article, which preceded Prinz and Geelhoed's reports on adrenal incidentaloma by a year, highlighted the uncertainties raised by incidentally discovered adrenal masses and their ensuing hormonal workup. Biochemical testing was indicated in patients with adrenal incidentaloma because the mass might secrete hormones, and adrenalectomy was performed in those patients with subclinical hormone secretion because they might develop future metabolic or physiologic problems even though they were currently symptom-free. With minimal existing evidence to guide them and little prior experience in dealing with this new class of patients, physicians were relying heavily on speculation and educated guesses to determine management; mostly, they were gearing their therapeutic decisions towards preventing the worst-case scenario, even though that scenario was extremely unlikely. When faced with the choice between action and inaction, they were erring on the side of action, even in completely asymptomatic patients such as Charbonnel's. Even in retrospect Charbonnel had not been able to state definitively whether operation had truly benefited his patient, but he leaned towards advocating operation for other patients who might be diagnosed with this form of "pre-Cushing's" syndrome. Subsequent authors would soon lend further weight to this recommendation.

The first case report of subclinical Cushing's syndrome from the U.S. was published in 1986 and was written by Stephen Beyer, an endocrinologist working

at the University of Minnesota.[43] The clinical history of Beyer's patient was quite similar to that presented in Charbonnel's paper: the patient was a 61-year old man with no outward manifestations of Cushing's syndrome who was found to have an adrenal mass on urography and CT scan, with mild abnormalities in cortisol levels and response to dexamethasone testing. His biochemical levels became normal after adrenalectomy. The tumor removed was found to be a benign cortical adenoma. Like Charbonnel, Beyer stated that it was not possible to predict whether his patient would have progressed to overt Cushing's syndrome if left untreated. However, Beyer emphasized that adrenalectomy was indicated not only because of the risk of future problems related to cortisol excess, but also because the tumor's cortisol secretion might have been a harbinger of malignancy, since adrenocortical cancers were known to frequently secrete cortisol. Even though the final specimen in this case was not found to be cancerous, Beyer speculated that the tumor may have been detected early enough to prevent both the development of Cushing's syndrome as well as possible adrenal cancer. His final analysis calls for the "improved definition of biochemical abnormalities that accompany apparently nonfunctional adrenal tumors" to "help clarify the role of surgical intervention," that is, more and better testing of patients with incidentally discovered adrenal tumors (which would inevitably lead to more operations).[44] As physicians became increasingly aware of adrenal incidentalomas and began uncovering subclinical hormone secretion during the course of working them up, they emphasized in print the dangerous

[43] H. S. Beyer and R. P. Doe, "Cortisol Secretion by an Incidentally Discovered Nonfunctional Adrenal Adenoma," J Clin Endocrinol Metab 62.6 (1986): 1317.
[44] Beyer, 1320.

possibilities that lurked within these seemingly innocuous masses; the “worst-case scenario” loomed larger and larger in physicians’ minds, and was beginning to overshadow the fact that the overwhelming majority of these tumors remained benign and nonfunctioning.

Beyer championed the benefits of early diagnosis of cortisol hypersecretion in preventing later complications and morbidity; other authors would soon report on the consequences of unrecognized subclinical Cushing’s syndrome in patients undergoing adrenalectomy. In a brief report in JAMA in 1989, Christopher Huiras, a surgeon in La Crosse, Wisconsin described two patients with adrenal incidentalomas and no signs of Cushing’s syndrome or other hormonal excess.[45] Laboratory testing included measurements of serum and urinary cortisol levels, which were within the normal range. Although biochemical testing revealed no abnormalities, the patients both underwent adrenalectomy because of concern for malignancy. To the surprise of the physicians caring for them, both patients developed postoperative adrenal insufficiency, which can lead to life-threatening shock if not treated immediately. Expeditious administration of glucocorticoids in both cases prevented further problems. Huiras attributed the unexpected findings of postoperative adrenal insufficiency in these two patients to low levels of excessive cortisol secretion by the adrenal tumors that went undetected by conventional serum or urinary tests; the cortisol levels were, however, significant enough to suppress the activity of the other adrenal gland. Once the enlarged adrenal tumor was removed, the

[45] C. M. Huiras, G. B. Pehling and R. H. Caplan, "Adrenal Insufficiency after Operative Removal of Apparently Nonfunctioning Adrenal Adenomas," JAMA 261.6 (1989): 894.

remaining adrenal gland was unable to produce enough cortisol to counteract the physiologic stress of operation, and the patient suffered the deleterious effects of adrenal insufficiency. Huiras believed that the existing serum and urinary tests for cortisol were not sensitive enough to pick up the low levels of secretion exhibited in these two cases, and urged clinicians to use the more sensitive dexamethasone suppression test when evaluating patients with adrenal incidentaloma and no obvious signs of Cushing's syndrome.[46] The two cases he presented served as a warning of the potentially life-threatening consequences of unanticipated subclinical Cushing's syndrome in patients with small, seemingly innocuous adrenal incidentalomas; Huiras stated at the end of his paper that "this situation [subclinical Cushing's syndrome] may be more common than previously appreciated" in the growing population of patients with adrenal incidentalomas.[47]

One noteworthy feature of Huiras' paper is his retrospective analysis of the clinical profiles of the two patients after the diagnosis of subclinical Cushing's syndrome had been made. One of the patients was truly asymptomatic, even in hindsight. The other patient was obese, hypertensive, and diabetic, findings commonly seen in patients with Cushing's. This patient's clinical presentation raises the question of whether she was truly "asymptomatic" or was exhibiting some of the end-organ manifestations of Cushing's syndrome without the other "classic" physical findings in the skin and body habitus. Huiras believed that the patient's obesity, hypertension, and diabetes were unrelated to Cushing's since her cortisol levels were so low and these problems did not resolve after

[46] Huiras, 896.
[47] Huiras, 897.

adrenalectomy,[48] but later authors would show that some of these clinical features were indeed caused by low levels of excess cortisol and could improve with adrenalectomy. In a 1992 paper German endocrinologist Martin Reincke presented eight patients (12% of all adrenal incidentalomas in his series) with subclinical Cushing's syndrome, all of whom had some combination of obesity, hypertension, and diabetes; these problems improved in the majority of his patients after adrenalectomy. Obesity, hypertension, and diabetes had previously been thought to be "normal" physiologic findings in "asymptomatic" patients with adrenal incidentalomas, but the growing body of knowledge and experience with these adrenal tumors was demonstrating that some of these patients where neither "normal" nor "asymptomatic," and would benefit from treatment for their previously unrecognized state of hormone excess. Clinicians were required to adjust their perceptions of how patients with Cushing's syndrome typically presented, as the diagnosis of mild, early disease became increasingly common. The face of the disease was changing.

Subclinical hormone secretion in patients with adrenal incidentalomas was not limited to cortisol. As endocrinologists performed increasing numbers of tests of hormonal secretion in patients with these tumors, they uncovered more examples of clinically silent hormone secretion. In his 1982 paper on his institution's initial experience with adrenal incidentalomas, Richard Prinz had discovered one patient with subclinical catecholamine secretion (pheochromocytoma).[49] Robert Caplan, an endocrinologist in La Crosse,

[48] Huiras, 896.
[49] Prinz, 702.

Wisconsin and co-author of the 1989 Huiras paper, reported in 1994 on 89 patients with adrenal incidentalomas, six of whom had subclinical hormone secretion.[50] The excess hormones detected included aldosterone in one patient, catecholamines in two patients, and cortisol in three patients. Caplan cautioned the surgeons and anesthesiologists performing operations on patients with adrenal incidentalomas to be prepared for intraoperative and postoperative problems related to unrecognized hormone excess, and cited one report of a patient who died after adrenalectomy from presumed adrenal insufficiency due to subclinical Cushing's syndrome.[51] Caplan also knew first-hand of a patient with unrecognized catecholamine secretion ("subclinical pheochromocytoma") who developed intraoperative hypertensive crisis during operation for a non-adrenal condition.[52] Hormonal testing of adrenal incidentalomas had been previously viewed as something of a formality, but as experience grew, this process was rapidly being recognized as a necessity to prevent some of the potential hazards of undiagnosed hormone hypersecretion.

Having advocated for routine hormonal testing of patients with adrenal incidentaloma even with the low expectation of positive findings in these otherwise "asymptomatic" patients, endocrinologists were now uncovering increasing numbers of patients with subclinical hormone secretion to justify these recommendations. Case series from the 1990s and 2000s documented

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[50] R. H. Caplan, P. J. Strutt and G. G. Wickus, "Subclinical Hormone Secretion by Incidentally Discovered Adrenal Masses," Arch Surg 129.3 (1994): 291.
[51] Caplan, 295.
[52] R. H. Caplan, W. A. Kisken and C. M. Huiras, "Incidentally Discovered Adrenal Masses," Minn Med 74.8 (1991): 23.

subclinical Cushing's syndrome in up to 20% of all adrenal incidentalomas, [53] and subclinical pheochromocytoma in approximately 5%.[54] The discovery of adrenal incidentaloma had revealed an entirely new class of patients with mild or nonexistent manifestations of adrenal hormone excess, and had altered the expectations of clinicians regarding the reasons for performing testing and the risks and benefits of treating patients with these seemingly innocuous adrenal tumors. Some unfortunate clinicians and patients had learned the consequences of undiagnosed subclinical hormone secretion in the form of intraoperative hypertensive crisis or postoperative adrenal insufficiency; some patients with adrenal incidentalomas who had previously thought of themselves as "asymptomatic" and even "healthy" had shown "improvement" in their clinical profiles after adrenalectomy. Endocrinologists debated some of the details regarding which patients would best benefit from treatment of unrecognized hormone hypersecretion, but overall referred increasing numbers of patients for operation during the decades following the discovery of adrenal incidentaloma and the subclinical hormone syndromes. Similar scenarios involving the early diagnosis and treatment of conditions of unknown significance have arisen in recent decades, including debates over pharmacologic therapy for mild hypertension, operation for asymptomatic hyperparathyroidism, and screening for prostate cancer using serum tests, and in almost all instances physicians have chosen to err on the side of intervention versus observation. The discovery of

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[53] A. Toniato, I. Merante-Boschin, G. Opocher, M. R. Pelizzo, F. Schiavi and E. Ballotta, "Surgical Versus Conservative Management for Subclinical Cushing Syndrome in Adrenal Incidentalomas: A Prospective Randomized Study," Ann Surg 249.3 (2009): 388.
[54] Young, 603.

subclinical hormone secretion syndromes in adrenal incidentaloma was no exception; concurrent efforts to establish the risk of malignancy in these tumors would add new layers of uncertainty and anxiety for physicians and tip the scales even further towards operation.

Chapter 3: Radiographic Assessment of Malignancy, Debates over Tumor Size, and the Impact of Laparoscopic Adrenalectomy

In the diagnostic workup of an incidentally discovered adrenal tumor, the burden of establishing whether these tumors exhibit hormonal hypersecretion falls primarily on endocrinologists; the task of determining the risk of malignancy is delegated mostly to physicians from the specialties of radiology and surgery. The combined input of these three disparate groups of medical specialists is required to fully characterize each adrenal incidentaloma and to make the ultimate decision regarding operation or observation for the patient. The following chapter focuses on the efforts of radiologists and surgeons to predict malignancy in adrenal incidentaloma in the decades following the initial discovery of this clinical entity. Endocrinologists had been required to formulate new diagnostic algorithms and adjust their definitions of adrenal disease during the course of working up hormonal hypersecretion; radiologists and surgeons faced similar problems in assessing the risk of malignancy, and responded with new strategies, technologies, and ways of thinking about the uncertainties raised by adrenal incidentaloma.

Radiologists had previously used adrenal imaging to confirm the presence of adrenal tumors in patients with biochemical or clinical evidence of adrenal hypersecretion or enlargement. With the introduction of CT scanning and its ability to identify previously unseen tumors, adrenal imaging now served as the point of entry, the “presenting complaint” for a growing number of patients

undergoing abdominal imaging for other indications. Radiologists were forced to utilize their expertise in order to characterize these tumors and provide the best possible assessment of malignancy. Short of removing the entire adrenal gland and performing microscopic histopathologic analysis (which itself is not wholly reliable), the determination of malignancy in a radiographically discovered adrenal tumor is fraught with difficulties. Fine-needle aspiration biopsy, which has high accuracy for diagnosing cancer in tumors of other organs such as the thyroid or breast, is only 50% accurate in distinguishing benign from malignant adrenal tumors.[55] In addition, fine-needle aspiration biopsy is technically demanding because of the adrenal gland's anatomic position in the retroperitoneum, may spill malignant cells into the abdominal cavity, and can precipitate life-threatening hypertensive crisis in patients with undiagnosed pheochromocytoma. No blood tests exist for determining adrenal malignancy. Data from autopsy series and early reports such as those by Prinz and Geelhoed had demonstrated that few nonfunctioning adrenal masses actually harbored cancer when removed via operation or when examined post-mortem. Primary adrenocortical carcinoma is an exceedingly rare disease, with an incidence of between one and two patients per one million population.[56] The consequences of not properly diagnosing a true adrenal cancer, however, are deadly: adrenocortical cancer has an aggressive growth pattern, propensity to metastasize, and a uniformly fatal prognosis if left untreated. Clinicians facing the

[55] F. J. Quayle, J. A. Spitler, R. A. Pierce, T. C. Lairmore, J. F. Moley and L. M. Brunt, "Needle Biopsy of Incidentally Discovered Adrenal Masses Is Rarely Informative and Potentially Hazardous," Surgery 142.4 (2007): 497.
[56] Shen, 190.

newly discovered problem of adrenal incidentaloma in the 1980s therefore sought a reliable, noninvasive means for establishing the risk of malignancy.

Radiologists of the era responded to the challenge of distinguishing benign from malignant adrenal tumors by recording detailed observations of tumor characteristics based upon their increasing experience with adrenal imaging, and also existing technology to establish objective, measurable criteria for estimating malignancy risk. Julie Mitnick and colleagues from the Department of Radiology at the New York University Medical Center published a paper in Radiology in 1983 detailing their experience in radiographic evaluation of 22 patients with adrenal incidentalomas using CT scanning.[57] Mitnick listed several observed features that appeared to correlate with benign adrenal pathology; these included smooth contours, well-demarcated borders, and round or oval shape. None of these features was unique to adrenal tumors, but could be applied to descriptions of benign tumors in many other organs. In addition to these descriptive features, Mitnick also provided a few objective criteria that suggested benign pathology: size less than 5 centimeters, no interval growth between serial scans, and tumor density measured with and without the administration of intravenous contrast.[58] The subjective and objective features that Mitnick described were intended to assist clinicians in assisting malignancy risk, with the overarching goal of preventing unnecessary operations in patients

[57] J. S. Mitnick, M. A. Bosniak, A. J. Megibow and D. P. Naidich, "Non-Functioning Adrenal Adenomas Discovered Incidentally on Computed Tomography," Radiology 148.2 (1983): 495.
[58] Mitnick, 496.

with adrenal incidentaloma, many of whom were elderly and could “ill-afford” the potential morbidity of open adrenalectomy.[59]

The standardized visual scale for estimating malignancy risk for adrenal incidentalomas that emerged from the work of radiologists such as Mitnick was based upon tumor tissue density as measured in Hounsfield units. The Hounsfield unit is a computer-derived measurement of radiodensity on CT imaging, with distilled water defined as representing 0 Hounsfield units (HU), air as -1000 HU, and bone as 400-1000 HU.[60] The scale was named after Sir Godfrey Hounsfield, co-inventor of CT scanning technology. Radiologists from the first days of CT scanning utilized tissue radiodensity in evaluating a variety of normal and pathologic structures. With refinements in CT technology and increased radiologist experience in interpreting the results of scans, more precise correlations between Hounsfield unit measurements and pathology were made for all types of benign and malignant tumors. The Hounsfield scale serves to quantify visual appearance in an easily communicated format that would be more difficult to describe using conventional language. Early papers and textbooks from the 1970s on CT imaging of the adrenal glands contain basic descriptions of Hounsfield unit measurements for adrenal tumors,[61] but it would take many more years for radiologists to establish numerical distinctions between benign, malignant and some types of hyperfunctioning adrenal tumors.

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[59] Mitnick, 499.
[60] I. Ilias, A. Sahdev, R. H. Reznek, A. B. Grossman and K. Pacak, "The Optimal Imaging of Adrenal Tumours: A Comparison of Different Methods," Endocr Relat Cancer 14.3 (2007): 587.
[61] E. G. Schaner, N. R. Dunnick, J. L. Doppman, C. A. Strott, J. R. Gill, Jr. and N. Javadpour, "Adrenal Cortical Tumors with Low Attenuation Coefficients: A Pitfall in Computed Tomography Diagnosis," J Comput Assist Tomogr 2.1 (1978): 11.

The most widely reported cutoffs for the radiographic diagnosis of adrenal tumors that emerged in the radiology literature following the initial recognition of adrenal incidentalomas in the early 1980s included the following: tumors measuring less than 10 HU are more likely to represent benign cortical adenomas, while tumors measuring greater than 20 HU are more likely to be either malignant or catecholamine-secreting (pheochromocytoma).[62] As might be expected, radiologists have not been in complete agreement with one another regarding the precise Hounsfield unit designations for adrenal tumors, and have demonstrated variability in density measurements depending on the type of scanner used and the timing of contrast administration.[63] Nonetheless, density measurements utilizing the Hounsfield scale became an accepted component of the algorithm for evaluating adrenal incidentalomas for radiologists, and non-radiologists would subsequently follow suit and adopt this standardized scale as well. “Hounsfield unit” is now a part of the normal vocabulary for discussing adrenal tumors for endocrinologists and surgeons alike; because the density measurement is generated by a computer, it is regarded as a value-free, objective measurement on par with a biochemical test result, and can therefore be plugged into a management algorithm or decision analysis more easily than a subjective, interpreter-dependent feature such as tumor heterogeneity or borders. In many cases the non-radiologist does not even have to actually “see”

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[62] F. E. Nwariaku, J. Champine, L. T. Kim, S. Burkey, G. O'Keefe and W. H. Snyder, 3rd, "Radiologic Characterization of Adrenal Masses: The Role of Computed Tomography-Derived Attenuation Values," Surgery 130.6 (2001): 1068.

[63] A. Stadler, W. Schima, G. Prager, P. Homolka, G. Heinz, S. Saini, E. Eisenhuber and B. Niederle, "CT Density Measurements for Characterization of Adrenal Tumors Ex Vivo: Variability among Three CT Scanners," AJR Am J Roentgenol 182.3 (2004): 671.

the CT scan to provide a radiographic assessment of the tumor in question, since the Hounsfield unit measurement is usually included in the radiologist's dictated report. However, as demonstrated by the attempts of endocrinologists to quantify hormonal secretion in these tumors, it is not entirely possible to utilize strict "black-and-white" designations for the decidedly "grey" entity of adrenal incidentaloma; the Hounsfield unit measurement is still regarded by many radiologists as too inaccurate to be used as a stand-alone criterion for recommending operation or observation for adrenal incidentaloma.[64] The Hounsfield unit allowed radiologists and their counterparts in endocrinology and surgery to incrementally reduce the level of uncertainty surrounding adrenal incidentaloma, but troublesome questions regarding the risk of malignancy in these tumors persisted.

While radiologists were attempting to refine their ability to predict malignancy in adrenal incidentalomas using radiographic features and Hounsfield unit measurements, surgeons debated where to set the appropriate cutoff for tumor size as an indication for operation. In the decades following the initial recognition of adrenal incidentaloma, surgeons exhibited varying levels of aggressiveness towards operating on patients with these tumors. As mentioned previously, open adrenalectomy consists of an abdominal or flank incision measuring at least several centimeters, results in significant postoperative pain, and requires several days in the hospital and several weeks of recuperation. Few, if any, surgeons disagreed with the prevailing recommendations that patients with clearly defined hormonal hypersecretion should undergo operation;

[64] Stadler, 674.

many also advocated for operation in patients with the subtle subclinical hormone secretion syndromes which were just being identified at the time.[65] Regarding small nonfunctioning adrenal masses, however, surgeons differed in their thresholds for recommending operation. Some surgeons agreed with the earliest management algorithm for adrenal incidentaloma, published by endocrinologist Paul Copeland in 1983, which recommended operation for tumors measuring 6 centimeters or greater, given the low overall likelihood of malignancy in smaller tumors and the comparatively high risk of morbidity with open adrenalectomy.[66] In a 1987 paper with the subheading “Is Operation for the Small Incidental Tumour Appropriate?”, Douglas Wood from the University of Sydney echoed Copeland’s measured approach and recommended a 6 centimeter cutoff for performing adrenalectomy.[67] Other surgeons during the same time period proposed incrementally lower tumor size thresholds for operation, including Miguel Herrera of the Mayo Clinic (4 centimeters),[68] Arie Belldegrun of the Brigham and Women’s Hospital (3.5 centimeters),[69] Edgar Staren of Rush University (3 centimeters),[70] and Michael Abecassis of the University of Toronto (2.5 centimeters).[71] In a 1985 article, J. Michael Seddon, a urologist from Marshall University in West Virginia, went so far as to recommend that surgeons

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[65] Caplan, “Subclinical Hormone Secretion,” 296.
[66] Copeland, 945.
[67] D. E. Wood, L. Delbridge and T. S. Reeve, "Surgery for Adrenal Tumours: Is Operation for the Small Incidental Tumour Appropriate?," Aust N Z J Surg 57.10 (1987): 739.
[68] M. F. Herrera, C. S. Grant, J. A. van Heerden, P. F. Sheedy and D. M. Ilstrup, "Incidentally Discovered Adrenal Tumors: An Institutional Perspective," Surgery 110.6 (1991): 1014.
[69] A. Belldegrun, S. Hussain, S. E. Seltzer, K. R. Loughlin, R. F. Gittes and J. P. Richie, "Incidentally Discovered Mass of the Adrenal Gland," Surg Gynecol Obstet 163.3 (1986): 203.
[70] E. D. Staren and R. A. Prinz, "Selection of Patients with Adrenal Incidentalomas for Operation," Surg Clin North Am 75.3 (1995): 499.
[71] M. Abecassis, M. J. McLoughlin, B. Langer and J. E. Kudlow, "Serendipitous Adrenal Masses: Prevalence, Significance, and Management," Am J Surg 149.6 (1985): 783.

consider performing adrenalectomy for all patients with adrenal incidentalomas, regardless of tumor size, stating that:

> "…in view of the questionable accuracy of radiologic diagnosis of adrenal masses and the well-documented difficulty in differentiating adrenal adenomas from carcinomas on histologic grounds, consideration should be given to surgical exploration and excision of all adrenal masses discovered incidentally."[72]

Evidently, surgeons had differing interpretations of what it meant to serve as "protector of the adrenal gland" as recommended by Glenn Geelhoed.

The seemingly short distance between 3 and 6 centimeters represented the zone of uncertainty for surgeons in deciding whether to operate on patients with adrenal incidentalomas. Where a surgeon drew the line for recommending operation was a reflection of how comfortable he or she was in dealing with the slim but real possibility that the adrenal mass in question harbored cancer. One could assure maximal certainty that no cancers were missed by adopting Seddon's approach and operating on all patients with adrenal incidentalomas; however, this strategy, besides being impractical, would expose large numbers of patients with benign tumors to unnecessary risks in order to benefit the exceedingly few patients with adrenocortical cancer (at most, 5% of all adrenal incidentalomas). Physicians were forced to "play the odds" when presented with patients with nonfunctioning adrenal incidentalomas in this 3-6 centimeter grey zone. When faced with the choice between action and inaction, most chose action, rather than living with the possibility of leaving a potentially malignant tumor inside the patient. Modern medical practice is inherently based on a series of these types of calculated decisions; the uncertainty generated weighs heavily

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[72] J. M. Seddon, N. Baranetsky and P. J. Van Boxel, "Adrenal 'Incidentalomas': Need for Surgery," Urology 25.1 (1985): 1.

on all parties involved in the decision process. As Miguel Herrera stated in his 1991 paper detailing the Mayo Clinic experience with adrenal incidentaloma, “the stakes are high, and the risks are borne by the patient.”[73]

In the midst of rapidly evolving understanding of subclinical hormone secretion, radiographic criteria for determining malignancy, and tumor size cutoffs for operation for adrenal incidentalomas, emerged the new technique of laparoscopic adrenalectomy, which would provide surgeons with a minimally invasive, less morbid approach towards removing adrenal tumors. As mentioned previously, open adrenalectomy requires a relatively large incision (with consequent postoperative pain), several days in the hospital, and weeks to months of recovery time. In contrast, laparoscopic adrenalectomy is performed through four to five 1-centimeter incisions, has less postoperative pain, and therefore results in shorter hospitalization and recovery time for patients. The initial reports of laparoscopic adrenalectomy were published in 1992; while a few surgeons claimed to be the first to perform the minimally invasive operation, most recognize Michel Gagner of the Hotel Dieu de Montreal as the originator of the technique. In a brief letter to the editor of the New England Journal of Medicine, Gagner described his initial experience with laparoscopic adrenalectomy in three patients (two with Cushing’s syndrome, one with pheochromocytoma).[74] Even at this early stage of his experience with the new technique, Gagner anticipated that laparoscopic adrenalectomy would prove useful for the growing number of patients with incidentally discovered adrenal tumors: he ended his letter by

[73] Herrera, 1020.
[74] M. Gagner, A. Lacroix and E. Bolte, "Laparoscopic Adrenalectomy in Cushing's Syndrome and Pheochromocytoma," N Engl J Med 327.14 (1992): 1033.

stating that “the decreased morbidity associated with this procedure may make it particularly helpful in the surgical management of asymptomatic adrenal lesions (‘incidentalomas’).”[75]

Following the introduction of laparoscopic adrenalectomy in 1992, surgeons around the world quickly adopted the technique; this was the time period in which minimally invasive operations as a whole began to flourish in several areas of surgery, with steep increases in the rates of laparoscopic cholecystectomy, appendectomy, and a variety of gynecologic and upper gastrointestinal tract operations. The rate of publications on the subject of laparoscopic adrenalectomy skyrocketed after Gagner’s initial publication, with 21 papers in 1993, 72 in 1999, 100 in 2001, and a peak of 136 in 2008. As Gagner had predicted, laparoscopic adrenalectomy was increasingly utilized for the removal of adrenal incidentalomas. One might expect that with the minimally invasive technique at their disposal, surgeons would become more willing to operate on patients with incidentally discovered adrenal tumors; in other words, the thresholds for operation would be lowered since the morbidity of the operation had been reduced. However, an examination of the literature of the time does not reveal any discrete changes in the published criteria for performing operation for adrenal incidentaloma. Surgeons still recommended operation for hormonal hypersecretion and for nonfunctioning tumors at tumor size cutoffs somewhere between 3 and 6 centimeters. Paolo Miccoli of the University of Pisa compared his case volume of adrenalectomies before and after he started using the laparoscopic technique and found that the number of operations he

[75] Gagner, 1033.

performed doubled after 1992.[76] The average tumor size remained the same (around 4 centimeters), but the percentage of patients with incidentalomas undergoing operation increased from 22% to 36%. Stan Sidhu of the Royal North Hospital in Sydney published similar data, with an increased number of operations being performed in his hospital after the introduction of the laparoscopic technique.[77] Both Miccoli and Sidhu believed that the increases in case numbers that they had observed were at least partially due to increased numbers of patients referred for operation by endocrinologists and other physicians. Even though there were no changes in the published criteria for operation, more patients with adrenal incidentalomas were finding their way to the surgeon's office. Miccoli believed that he and his referring physicians had not changed their standards for selecting patients for operation even after the introduction of the laparoscopic technique: "it is concluded that availability of a laparoscopic approach does not lead to surgeons and endocrinologists overtreating their patients."[78]

If the published criteria for recommending surgery did not change, what factors led to the increased numbers of patients undergoing operation for adrenal incidentaloma after 1992? First off, more patients with being diagnosed with adrenal incidentalomas because of the increasing utilization of abdominal CT scans. As mentioned by Miccoli and Sidhu, endocrinologists appeared to be

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[76] P. Miccoli, M. Raffaelli, P. Berti, G. Materazzi, M. Massi and G. Bernini, "Adrenal Surgery Before and After the Introduction of Laparoscopic Adrenalectomy," Br J Surg 89.6 (2002): 779.
[77] S. Sidhu, C. Bambach, S. Pillinger, T. Reeve, G. Stokes, B. Robinson and L. Delbridge, "Changing Pattern of Adrenalectomy at a Tertiary Referral Centre 1970-2000," ANZ J Surg 72.7 (2002): 463.
[78] Miccoli, 781.

more willing to refer patients with adrenal incidentalomas for operation now that a less painful and morbid means for removing adrenal tumors had been introduced. Many non-surgeon physicians were quick to recognize the benefits of laparoscopic adrenalectomy and wrote of the technique in a favorable light; German endocrinologist Stefan Bornstein went so far as to describe the operation as “non-invasive” in 2002.[79] Surgeons certainly appeared to be more willing to perform laparoscopic adrenalectomy, mostly because the approach was better for patients overall; however, one cannot underestimate the additional impact of the general enthusiasm of surgeons around the world for all forms of minimally invasive operations during the 1990s. Adrenalectomy was particularly well-suited for the laparoscopic technique because of the relatively inaccessible location of the adrenal glands, and had been lauded by surgeons as an “elegant”[80] means for accomplishing the task of removing adrenal tumors. An additional factor contributing to the increased number of adrenalectomies performed was the willingness of patients to undergo the laparoscopic operation when presented with that option as compared with the open approach, with its attendant pain and lengthy recovery. Lastly, I would argue that one of the most important reasons for the increased number of adrenalectomies being performed after 1992 was the overall heightened awareness of the adrenal glands and adrenal disease amongst endocrinologists, radiologists and surgeons of that period of time. As evidenced by the profusion of research and publications by

[79] National Institutes of Health, Program and Abstracts, 18.
[80] G. Hofle, R. W. Gasser, K. Lhotta, G. Janetschek, A. Kreczy and G. Finkenstedt, "Adrenocortical Carcinoma Evolving after Diagnosis of Preclinical Cushing's Syndrome in an Adrenal Incidentaloma: A Case Report," Horm Res 50.4 (1998): 237.

physicians attempting to better understand and treat adrenal incidentalomas following the initial recognition of this entity in 1982, increasing numbers of patients were being diagnosed with asymptomatic adrenal masses, evaluated for hormonal hypersecretion, and referred for operation, especially after the laparoscopic approach was introduced. As Paul Copeland had predicted in 1983, in recognizing adrenal incidentaloma, physicians had created “an iatrogenic disease of medical progress”[81] and were now inundated with ever-increasing numbers of patients with these incidentally discovered tumors of uncertain significance.

[81] Copeland, 940.

Chapter 4: Answers and Questions from the 2002 NIH Consensus Conference, and Reflections on the Impact of Adrenal Incidentaloma

By the time the NIH held its two-and-a-half day consensus conference on the "clinically inapparent adrenal mass" in February, 2002, physicians around the world were well aware of the existence of adrenal incidentaloma and had been seeking to improve its understanding and treatment for nearly twenty years. From the initial case reports of Prinz and Geelhoed had emerged an entirely new field of research and practice, as well as a continually increasing population of patients who required diagnostic workup and possible operation. The phenomenon of incidentally discovered tumors had spread to include other organs such as the pituitary, thyroid, pancreas, and liver; there are now very few areas of the body that are inaccessible to radiographic imaging, and therefore very few areas of the body that have not been found to harbor asymptomatic, previously unrecognized tumors. Endocrinologist David Aron of Case Western Reserve University estimates that 25% of his current practice consists of patients with incidentally discovered tumors of endocrine organs.[82] The 2002 NIH consensus conference served as a means for consolidating the vast amount of information that had been produced on adrenal incidentaloma in the short period of time since its initial discovery, and for producing rational management guidelines using the best evidence available.

After listening to the 21 invited speakers give their talks on a spectrum of issues related to incidentally discovered adrenal tumors, the 12-member panel

[82] David Aron, telephone interview with author, 31 March 2009.

broke off into smaller sub-groups, each charged with reviewing a specific set of questions and drafting recommendations based upon the preceding talks as well as their own readings on the subjects.[83] Grumbach recalls little controversy in the ensuing discussions.[84] The sub-groups reconvened after several hours to compose the final consensus guidelines. Although they worked until early the next morning, they were able to meet their self-imposed deadline: at 9AM on February 6th, 2002, the panel presented their state-of-the science statement on the "clinically inapparent adrenal mass." The text of the guidelines was available on the internet by later that morning.[85]

The final recommendations of the NIH panel did not deviate much from the existing algorithms in the literature, but they provided a single authoritative source for practitioners to reference, and laid the groundwork for the next wave of research in the field of adrenal incidentaloma. The panel recognized the importance of diagnosing subclinical hormone secretion and recommended that all patients with incidentally discovered adrenal masses be tested for cortisol and catecholamine hypersecretion, as these were the subclinical syndromes most commonly encountered (and were also potentially life-threatening if unrecognized in a patient undergoing adrenalectomy). Operation was recommended for all patients with pheochromocytoma, but the panel withheld final judgment on the utility of operation for subclinical Cushing's, stating that "data are insufficient to

[83] Grumbach, interview with author.
[84] Grumbach, interview with author.
[85] National Institutes of Health, "NIH State-of-the-Science Statement on Management of the Clinically Inapparent Adrenal Mass ('Incidentaloma')," NIH Consens State Sci Statements 19.2 (2002): ii.

indicate the superiority of a surgical or nonsurgical approach;"[86] nonetheless, they referenced several studies demonstrating benefit for patients diagnosed with subclinical Cushing's who underwent adrenalectomy. The Hounsfield unit cutoff of <10 HU was mentioned briefly as indicating that an adrenal tumor was "likely a benign adenoma,"[87] but the panel did not lend much further credence to the use of tumor density measurements for determining malignancy. The panel did not significantly narrow the previously published "grey zone" of tumor size cutoffs for recommending operation; they advocated operation for tumors >6 centimeters, observation for nonfunctioning tumors <4 centimeters, and consideration of "criteria in addition to size"[88] for tumors between 4 and 6 centimeters. In regards to the choice of operative approach, the panel stated that both the open and laparoscopic techniques were acceptable, but cited the advantages of laparoscopic adrenalectomy "when performed by a surgical team experienced in advanced laparoscopic techniques."[89]

The NIH consensus panel concluded its "state-of-the-science" statement by challenging researchers to address and answer several unresolved questions regarding adrenal incidentalomas. First off, they highlighted the "paucity of evidence-based data"[90] on adrenal incidentalomas, since almost all of the existing information had come from small, retrospectively procured institutional series, and called for the "establishment of an international collaborative study group whose charge would be to develop a database of patients with clinically

[86] National Institutes of Health, "State-of-the-Science Statement," 2.
[87] National Institutes of Health, "State-of-the-Science Statement," 2.
[88] National Institutes of Health, "State-of-the-Science Statement," 3.
[89] National Institutes of Health, "State-of-the-Science Statement," 14.
[90] National Institutes of Health, "State-of-the-Science Statement," 3.

inapparent adrenal masses."[91] The subsequent questions suggested by the panel included improved understanding of the natural history of untreated nonfunctioning adrenal tumors; more precise clinical and radiographic predictors of malignancy risk; better guidelines for following patients with unresected tumors; and prospective studies of operative and nonoperative management of subclinical Cushing's syndrome. Perhaps most interestingly, the panel recommended research on the psychosocial effects of adrenal incidentalomas on the patients in whom these tumors are diagnosed; the emotional impact on otherwise healthy patients of learning about a clinically silent adrenal tumor, making decisions regarding operation and observation, and living with the possibility of developing cancer in an unresected tumor had been relatively ignored in the previous two decades' worth of research on the subject. Also noteworthy in the concluding paragraph of the NIH guidelines is the panel's reference to adrenal incidentaloma as a "common condition."[92] What had started as an infrequent "accidental" finding just two decades prior was now considered an expected consequence of modern medical imaging techniques.

Endocrinologist David Aron has written extensively on the subject of adrenal incidentaloma and has frequently referred to it as a "disease of modern technology."[93] In his articles he has demonstrated how physicians routinely overestimate the risk of malignancy and hormonal activity in patients with adrenal incidentalomas, thereby resulting in excessive, unnecessary testing and operations in a large number of otherwise healthy patients with benign adrenal

[91] National Institutes of Health, "State-of-the-Science Statement," 16.
[92] National Institutes of Health, "State-of-the-Science Statement," 18.
[93] Chidiac, 233.

tumors. While there appear to be benefits of early diagnosis in the minority of patients with true subclinical hormone secretion or malignant tumors, Aron states emphatically that “our ability to accurately determine clinically those at increased risk among the vast majority who are not at increased risk is poor.”[94] Aron and outcomes researcher Richard Deyo of Oregon Health Sciences University have both touted adrenal incidentaloma as a prime example of the “cascade effect” in modern medical practice.[95] Initially described by Richard Mold in 1986,[96] the cascade effect is defined as a series of clinical events triggered by a single finding, often catalyzed by physician or patient anxiety. Other types of clinical cascades described by Deyo include fetal heart monitoring resulting in increased rates of Caesarean sections, and increased utilization of spinal MRI leading to high rates of spinal surgery with minimal demonstrable benefits.[97] The inevitable series of biochemical and radiographic tests and the frequent recommendations for adrenalectomy following the initial unsolicited finding of adrenal incidentaloma fit the description of a clinical cascade well. Aron, Deyo, and Molds all conclude that physicians need to become better aware of the clinical cascades that they generate in practice every day, and that improved understanding of the reasons for ordering tests and performing invasive procedures may be the key to ensuring more judicious decisions regarding sources of uncertainty such as adrenal incidentaloma.

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[94] D. C. Aron, "The Adrenal Incidentaloma: Disease of Modern Technology and Public Health Problem," Rev Endocr Metab Disord 2.3 (2001): 342.
[95] R. A. Deyo, "Cascade Effects of Medical Technology," Annu Rev Public Health 23 (2002): 23.
[96] J. W. Mold and H. F. Stein, "The Cascade Effect in the Clinical Care of Patients," N Engl J Med 314.8 (1986): 512.
[97] Deyo, 23.

The constant tension underlying the history of adrenal incidentaloma hinges on physicians' ability to deal with uncertainty in a practice environment where they are increasingly expected to provide black-and-white opinions and high-quality, error-free care. After more than two decades of research and a exhaustive review by an NIH consensus panel, the process of characterizing the hormonal profile and malignant potential of an adrenal incidentaloma is still laden with speculation and guesswork. In a 1989 New England Journal of Medicine article entitled "Our Stubborn Quest for Diagnostic Uncertainty," Jerome Kassirer wrote that physicians must come to terms with the fact that their primary objective is "not to attain certainty, but rather to reduce the level of diagnostic uncertainty to make optimal therapeutic decisions."[98] The story of adrenal incidentaloma highlights some of the difficulties of achieving this delicate balance between certainty and uncertainty in modern medicine. The introduction of the new imaging technology of CT scanning undoubtedly improved the diagnostic capabilities of radiologists and other physicians, but uncovered the new clinical entity of adrenal incidentaloma and left clinicians with unexpected uncertainty and an entirely new population of patients requiring workup and treatment. A subgroup of these patients with subclinical hormone secretion was found to benefit from early detection and operation. However, a much larger group of patients remains in diagnostic limbo, and in many cases physicians have chosen to act rather than observe. Thousands of adrenalectomies for benign nonfunctioning tumors continue to be performed each year. The public health

[98] J. P. Kassirer, "Our Stubborn Quest for Diagnostic Certainty: A Cause of Excessive Testing," N Engl J Med 320.22 (1989): 1489.

costs of these unnecessary operations are enormous: a recent report in JAMA estimated that greater than 12,000 patients die in the U.S. each year from complications of operations that in retrospect are deemed unnecessary.[99] Endocrinologists, radiologists, and surgeons have made great strides in understanding the clinical entity of adrenal incidentaloma, but have much room for improvement in their roles as “protectors” of the adrenal gland.

[99] B. Starfield, "Is U.S. Health Really the Best in the World?," JAMA 284.4 (2000): 483.

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