CANCERGENOMICS
www.sciencemag.org/special/cancergenomics

REVIEW

Cancer Genome Landscapes

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Over the past decade, comprehensive sequencing efforts have revealed the genomic landscapes of common forms of human cancer. For most cancer types, this landscape consists of a small number of "mountains" (genes altered in a high percentage of tumors) and a much larger number of "hills" (genes altered infrequently). To date, these studies have revealed ~140 genes that, when altered by intragenic mutations, can promote or "drive" tumorigenesis. A typical tumor contains two to eight of these "driver gene" mutations; the remaining mutations are passengers that confer no selective growth advantage. Driver genes can be classified into 12 signaling pathways that regulate three core cellular processes: cell fate, cell survival, and genome maintenance. A better understanding of these pathways is one of the most pressing needs in basic cancer research. Even now, however, our knowledge of cancer genomes is sufficient to guide the development of more effective approaches for reducing cancer morbidity and mortality.

Ten years ago, the idea that all of the genes altered in cancer could be identified at base-pair resolution would have seemed like science fiction. Today, such genome-wide analysis, through sequencing of the exome (see Box 1, Glossary, for definitions of terms used in this Review) or of the whole genome, is routine.

The prototypical exomic studies of cancer evaluated ~20 tumors at a cost of >$100,000 per case (*1*–*3*). Today, the cost of this sequencing has been reduced 100-fold, and studies reporting the sequencing of more than 100 tumors of a given type are the norm (table S1A). Although vast amounts of data can now be readily obtained, deciphering this information in meaningful terms is still challenging. Here, we review what has been learned about cancer genomes from these sequencing studies—and, more importantly, what this information has taught us about cancer biology and future cancer management strategies.

How Many Genes Are Subtly Mutated in a Typical Human Cancer?

In common solid tumors such as those derived from the colon, breast, brain, or pancreas, an average of 33 to 66 genes display subtle somatic mutations that would be expected to alter their protein products (Fig. 1A). About 95% of these mutations are single-base substitutions (such as C>G), whereas the remainder are deletions or insertions of one or a few bases (such as CTT>CT) (table S1B). Of the base substitutions, 90.7% result in missense changes, 7.6% result in nonsense changes, and 1.7% result in alterations of splice sites or untranslated regions immediately adjacent to the start and stop codons (table S1B).

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Certain tumor types display many more or many fewer mutations than average (Fig. 1B). Notable among these outliers are melanomas and lung tumors, which contain ~200 nonsynonymous mutations per tumor (table S1C). These larger numbers reflect the involvement of potent mutagens (ultraviolet light and cigarette smoke, respectively) in the pathogenesis of these tumor types. Accordingly, lung cancers from smokers have 10 times as many somatic mutations as those from nonsmokers (*4*). Tumors with defects in DNA repair form another group of outliers (*5*). For example, tumors with mismatch repair defects can harbor thousands of mutations (Fig. 1B), even more than lung tumors or melanomas. Recent studies have shown that high numbers of mutations are also found in tumors with genetic alterations of the proofreading domain of DNA polymerases POLE or POLD1 (*6*, *7*). At the other end of the spectrum, pediatric tumors and leukemias harbor far fewer point mutations: on average, 9.6 per tumor (table S1C). The basis for this observation is considered below.

Mutation Timing

When do these mutations occur? Tumors evolve from benign to malignant lesions by acquiring a series of mutations over time, a process that has been particularly well studied in colorectal tumors (*8*, *9*). The first, or "gatekeeping," mutation provides a selective growth advantage to a normal epithelial cell, allowing it to outgrow the cells that surround it and become a microscopic clone (Fig. 2). Gatekeeping mutations in the colon most often occur in the *APC* gene (*10*). The small adenoma that results from this mutation grows slowly, but a second mutation in another gene, such as *KRAS*, unleashes a second round of clonal growth that allows an expansion of cell number (*9*). The cells with only the *APC* mutation may persist, but their cell numbers are small compared with the cells that have mutations in both genes. This process of mutation followed by clonal expansion continues, with mutations in genes such as *PIK3CA*, *SMAD4*, and *TP53*, eventually generating a malignant tumor that can invade through the underlying basement membrane and metastasize to lymph nodes and distant organs such as the liver (*11*). The mutations that confer a selective growth advantage to the tumor cell are called "driver" mutations. It has been estimated (*12*) that each driver mutation provides only a small selective growth advantage to the cell, on the order of a 0.4% increase in the difference between cell birth and cell death. Over many years, however, this slight increase, compounded once or twice per week, can result in a large mass, containing billions of cells.

The number of mutations in certain tumors of self-renewing tissues is directly correlated with age (*13*). When evaluated through linear regression, this correlation implies that more than half of the somatic mutations identified in these tumors occur during the preneoplastic phase; that is, during the growth of normal cells that continuously replenish gastrointestinal and genitourinary epithelium and other tissues. All of these pre-neoplastic mutations are "passenger" mutations that have no effect on the neoplastic process. This result explains why a colorectal tumor in a 90-year-old patient has nearly twice as many mutations as a morphologically identical colorectal tumor in a 45-year-old patient. This finding also partly explains why advanced brain tumors (glioblastomas) and pancreatic cancers (pancreatic ductal adenocarcinomas) have fewer mutations than colorectal tumors; glial cells of the brain and epithelial cells of the pancreatic ducts do not replicate, unlike the epithelial cells lining the crypts of the colon. Therefore, the gatekeeping mutation in a pancreatic or brain cancer is predicted to occur in a precursor cell that contains many fewer mutations than are present in a colorectal precursor cell. This line of reasoning also helps to explain why pediatric cancers have fewer mutations than adult tumors. Pediatric cancers often occur in non–self-renewing tissues, and those that arise in renewing tissues (such as leukemias) originate from precursor cells that have not renewed themselves as often as in adults. In addition, pediatric tumors, as well as adult leukemias and lymphomas, may require fewer rounds of clonal expansion than adult solid tumors (*8*, *14*). Genome sequencing studies of leukemia patients support the idea that mutations occur as random events in normal precursor cells before these cells acquire an initiating mutation (*15*).

When during tumorigenesis do the remaining somatic mutations occur? Because mutations in tumors occur at predictable and calculable rates (see below), the number of somatic mutations in tumors provides a clock, much like the clock used in evolutionary biology to determine species

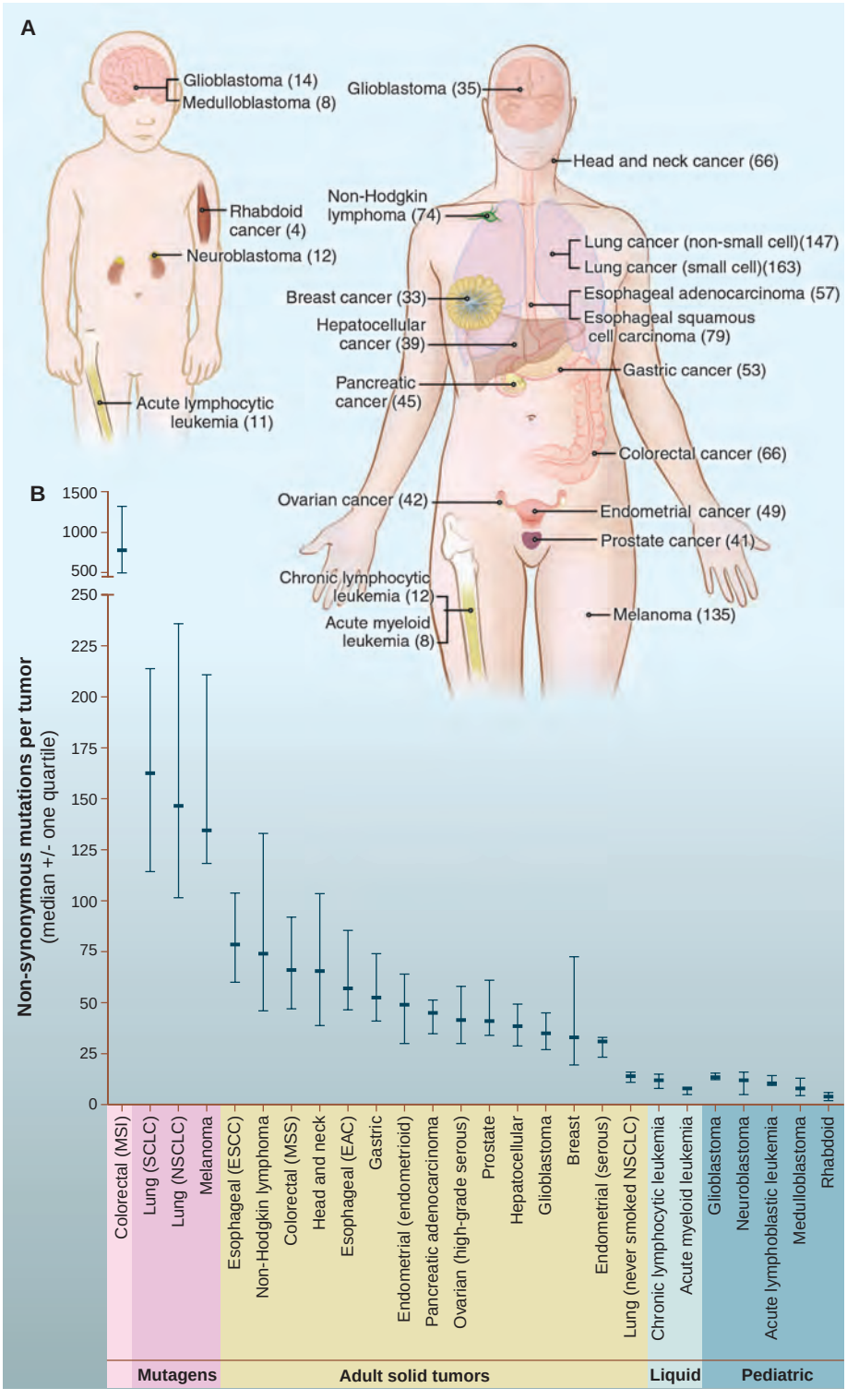

Fig. 1. Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies. (**A**) The genomes of a diverse group of adult (right) and pediatric (left) cancers have been analyzed. Numbers in parentheses indicate the median number of nonsynonymous mutations per tumor. (**B**) The median number of nonsynonymous mutations per tumor in a variety of tumor types. Horizontal bars indicate the 25 and 75% quartiles. MSI, microsatellite instability; SCLC, small cell lung cancers; NSCLC, non–small cell lung cancers; ESCC, esophageal squamous cell carcinomas; MSS, microsatellite stable; EAC, esophageal adenocarcinomas. The published data on which this figure is based are provided in table S1C.

CREDIT: FIG. 1A, E. COOK

divergence time. The number of mutations has been measured in tumors representing progressive stages of colorectal and pancreatic cancers (*11*, *16*). Applying the evolutionary clock model to these data leads to two unambiguous conclusions: First, it takes decades to develop a full-blown, metastatic cancer. Second, virtually all of the mutations in metastatic lesions were already present in a large number of cells in the primary tumors.

The timing of mutations is relevant to our understanding of metastasis, which is responsible for the death of most patients with cancer. The primary tumor can be surgically removed, but the residual metastatic lesions—often undetectable and widespread—remain and eventually enlarge, compromising the function of the lungs, liver, or other organs. From a genetics perspective, it would seem that there must be mutations that convert a primary cancer to a metastatic one, just as there are mutations that convert a normal cell to a benign tumor, or a benign tumor to a malignant one (Fig. 2). Despite intensive effort, however, consistent genetic alterations that distinguish cancers that metastasize from cancers that have not yet metastasized remain to be identified.

One potential explanation invokes mutations or epigenetic changes that are difficult to identify with current technologies (see section on "dark matter" below). Another explanation is that metastatic lesions have not yet been studied in sufficient detail to identify these genetic alterations, particularly if the mutations are heterogeneous in nature. But another possible explanation is that there are no metastasis genes. A malignant primary tumor can take many years to metastasize, but this process is, in principle, explicable by stochastic processes alone (*17*, *18*). Advanced tumors release millions of cells into the circulation each day, but these cells have short half-lives, and only a miniscule fraction establish metastatic lesions (*19*). Conceivably, these circulating cells may, in a nondeterministic manner, infrequently and randomly lodge in a capillary bed in an organ that provides a favorable microenvironment for growth. The bigger the primary tumor mass, the more likely that this process will occur. In this scenario, the continual evolution of the primary tumor would reflect local selective advantages rather than future selective advantages. The idea that growth at metastatic sites is not dependent on additional genetic alterations is also supported by recent results showing that even normal cells, when placed in suitable environments such as lymph nodes, can grow into organoids, complete with a functioning vasculature (*20*).

Other Types of Genetic Alterations in Tumors

Though the rate of point mutations in tumors is similar to that of normal cells, the rate of chromosomal changes in cancer is elevated (*21*). Therefore, most solid tumors display widespread changes in chromosome number (aneuploidy), as well as deletions, inversions, translocations,

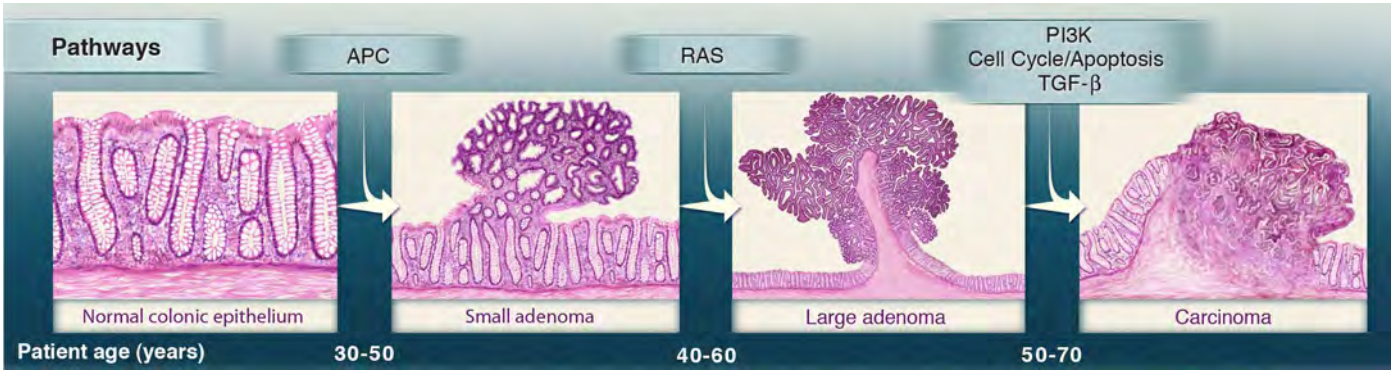

Fig. 2. Genetic alterations and the progression of colorectal cancer. The major signaling pathways that drive tumorigenesis are shown at the transitions between each tumor stage. One of several driver genes that encode components of these pathways can be altered in any individual tumor. Patient age indicates the time intervals during which the driver genes are usually mutated. Note that this model may not apply to all tumor types. TGF-β, transforming growth factor–β.

and other genetic abnormalities. When a large part of a chromosome is duplicated or deleted, it is difficult to identify the specific "target" gene(s) on the chromosome whose gain or loss confers a growth advantage to the tumor cell. Target genes are more easily identified in the case of chromosome translocations, homozygous deletions, and gene amplifications. Translocations generally fuse two genes to create an oncogene (such as *BCR-ABL* in chronic myelogenous leukemia) but, in a small number of cases, can inactivate a tumor suppressor gene by truncating it or separating it from its promoter. Homozygous deletions often involve just one or a few genes, and the target is always a tumor suppressor gene. Amplifications contain an oncogene whose protein product is abnormally active simply because the tumor cell contains 10 to 100 copies of the gene per cell, compared with the two copies present in normal cells.

Most solid tumors have dozens of translocations; however, as with point mutations, the majority of translocations appear to be passengers rather than drivers. The breakpoints of the translocations are often in "gene deserts" devoid of known genes, and many of the translocations and homozygous deletions are adjacent to fragile sites that are prone to breakage. Cancer cells can, perhaps, survive such chromosome breaks more easily than normal cells because they contain mutations that incapacitate genes like *TP53*, which would normally respond to DNA damage by triggering cell death. Studies to date indicate that there are roughly 10 times fewer genes affected by chromosomal changes than by point mutations. Figure 3 shows the types and distribution of genetic alterations that affect protein-coding genes in five representative tumor types. Protein-coding genes account for only ~1.5% of the total genome, and the number of alterations in noncoding regions is proportionately higher than the number affecting coding regions. The vast majority of the alterations in noncoding regions are presumably passengers. These noncoding mutations, as well as the numerous epigenetic changes found in cancers, will be discussed later.

Drivers Versus Passenger Mutations

Though it is easy to define a "driver gene mutation" in physiologic terms (as one conferring a selective growth advantage), it is more difficult to identify which somatic mutations are drivers and which are passengers. Moreover, it is important to point out that there is a fundamental difference between a driver gene and a driver gene mutation. A driver gene is one that contains driver gene mutations. But driver genes may also contain passenger gene mutations. For example, *APC* is a large driver gene, but only those mutations that truncate the encoded protein within its N-terminal 1600 amino acids are driver gene mutations. Missense mutations throughout the gene, as well as protein-truncating mutations in the C-terminal 1200 amino acids, are passenger gene mutations.

Numerous statistical methods to identify driver genes have been described. Some are based on the frequency of mutations in an individual gene compared with the mutation frequency of other genes in the same or related tumors after correction for sequence context and gene size (*22*, *23*). Other methods are based on the predicted effects of mutation on the encoded protein, as inferred from biophysical studies (*24*–*26*). All of these methods are useful for prioritizing genes that are most likely to promote a selective growth advantage when mutated. When the number of mutations in a gene is very high, as with *TP53* or *KRAS*, any reasonable statistic will indicate that the gene is extremely likely to be a driver gene. These highly mutated genes have been termed "mountains" (*1*). Unfortunately, however, genes with more than one, but still relatively few mutations (so called "hills") numerically dominate cancer genome landscapes (*1*). In these cases, methods based on mutation frequency and context alone cannot reliably indicate which genes are drivers, because the background rates of mutation vary so much among different patients and regions of the genome. Recent studies of normal cells have indicated that the rate of mutation varies by more than 100-fold within the genome (*27*). In tumor cells, this variation can be higher and may affect whole

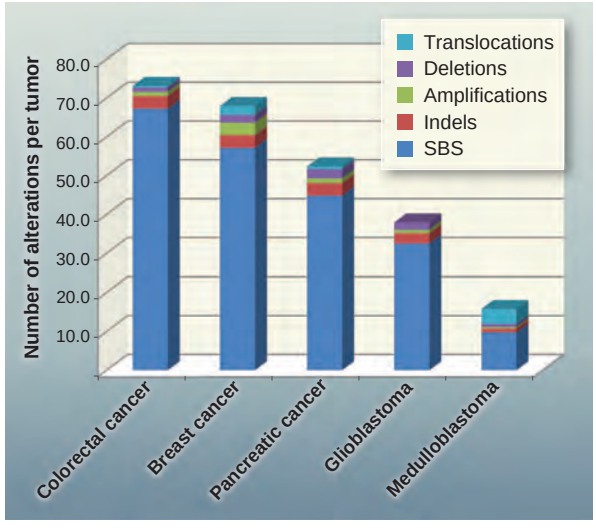

Fig. 3. Total alterations affecting protein-coding genes in selected tumors. Average number and types of genomic alterations per tumor, including single-base substitutions (SBS), small insertions and deletions (indels), amplifications, and homozygous deletions, as determined by genome-wide sequencing studies. For colorectal, breast, and pancreatic ductal cancer, and medulloblastomas, translocations are also included. The published data on which this figure is based are provided in table S1D.

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Box 1. Glossary

Adenoma: A benign tumor composed of epithelial cells.

Alternative lengthening of telomeres (ALT): A process of maintaining telomeres independent of telomerase, the enzyme normally responsible for telomere replication.

Amplification: A genetic alteration producing a large number of copies of a small segment (less than a few megabases) of the genome.

Angiogenesis: the process of forming vascular conduits, including veins, arteries, and lymphatics.

Benign tumor: An abnormal proliferation of cells driven by at least one mutation in an oncogene or tumor suppressor gene. These cells are not invasive (i.e., they cannot penetrate the basement membrane lining them), which distinguishes them from malignant cells.

Carcinoma: A type of malignant tumor composed of epithelial cells.

Clonal mutation: A mutation that exists in the vast majority of the neoplastic cells within a tumor.

Driver gene mutation (driver): A mutation that directly or indirectly confers a selective growth advantage to the cell in which it occurs.

Driver gene: A gene that contains driver gene mutations (Mut-Driver gene) or is expressed aberrantly in a fashion that confers a selective growth advantage (Epi-Driver gene).

Epi-driver gene: A gene that is expressed aberrantly in cancers in a fashion that confers a selective growth advantage.

Epigenetic: Changes in gene expression or cellular phenotype caused by mechanisms other than changes in the DNA sequence.

Exome: The collection of exons in the human genome. Exome sequencing generally refers to the collection of exons that encode proteins.

Gatekeeper: A gene that, when mutated, initiates tumorigenesis. Examples include *RB*, mutations of which initiate retinoblastomas, and *VHL*, whose mutations initiate renal cell carcinomas.

Germline genome: An individual's genome, as inherited from their parents.

Germline variants: Variations in sequences observed in different individuals. Two randomly chosen individuals differ by ~20,000 genetic variations distributed throughout the exome.

Human leukocyte antigen (HLA): A protein encoded by genes that determine an individual's capacity to respond to specific antigens or reject transplants from other individuals.

Homozygous deletion: Deletion of both copies of a gene segment (the one inherited from the mother, as well as that inherited from the father).

Indel: A mutation due to small insertion or deletion of one or a few nucleotides.

Karyotype: Display of the chromosomes of a cell on a microscopic slide, used to evaluate changes in chromosome number as well as structural alterations of chromosomes.

Kinase: A protein that catalyzes the addition of phosphate groups to other molecules, such as proteins or lipids. These proteins are essential to nearly all signal transduction pathways.

Liquid tumors: Tumors composed of hematopoietic (blood) cells, such as leukemias. Though lymphomas generally form solid masses in lymph nodes, they are often classified as liquid tumors because of their derivation from hematopoietic cells and ability to travel through lymphatics.

Malignant tumor: An abnormal proliferation of cells driven by mutations in oncogenes or tumor suppressor genes that has already invaded their surrounding stroma. It is impossible to distinguish an isolated benign tumor cell from an isolated malignant tumor cell. This distinction can be made only through examination of tissue architecture.

Metastatic tumor: A malignant tumor that has migrated away from its primary site, such as to draining lymph nodes or another organ.

Methylation: Covalent addition of a methyl group to a protein, DNA, or other molecule.

Missense mutation: A single-nucleotide substitution (e.g., C to T) that results in an amino acid substitution (e.g., histidine to arginine).

Mut-driver gene: A gene that contains driver gene mutations.

Nonsense mutation: A single-nucleotide substitution (e.g., C to T) that results in the production of a stop codon.

Nonsynonymous mutation: A mutation that alters the encoded amino acid sequence of a protein. These include missense, nonsense, splice site, translation start, translation stop, and indel mutations.

Oncogene: A gene that, when activated by mutation, increases the selective growth advantage of the cell in which it resides.

Passenger mutation (passenger): A mutation that has no direct or indirect effect on the selective growth advantage of the cell in which it occurred.

Primary tumor: The original tumor at the site where tumor growth was initiated. This can be defined for solid tumors, but not for liquid tumors.

Promoter: A region within or near the gene that helps regulate its expression.

Rearrangement: A mutation that juxtaposes nucleotides that are normally separated, such as those on two different chromosomes.

Selective growth advantage (*s*): The difference between birth and death in a cell population. In normal adult cells in the absence of injury, $s = 0.000000$.

Self-renewing tissues: Tissues whose cells normally repopulate themselves, such as those lining the gastrointestinal or urogenital tracts, as well as blood cells.

Single-base substitution (SBS): A single-nucleotide substitution (e.g., C to T) relative to a reference sequence or, in the case of somatic mutations, relative to the germline genome of the person with a tumor.

Solid tumors: Tumors that form discrete masses, such as carcinomas or sarcomas.

Somatic mutations: Mutations that occur in any non–germ cell of the body after conception, such as those that initiate tumorigenesis.

Splice sites: Small regions of genes that are juxtaposed to the exons and direct exon splicing.

Stem cell: An immortal cell that can repopulate a particular cell type.

Subclonal mutation: A mutation that exists in only a subset of the neoplastic cells within a tumor.

Translocation: A specific type of rearrangement where regions from two nonhomologous chromosomes are joined.

Tumor suppressor gene: A gene that, when inactivated by mutation, increases the selective growth advantage of the cell in which it resides.

Untranslated regions: Regions within the exons at the 5′ and 3′ ends of the gene that do not encode amino acids.

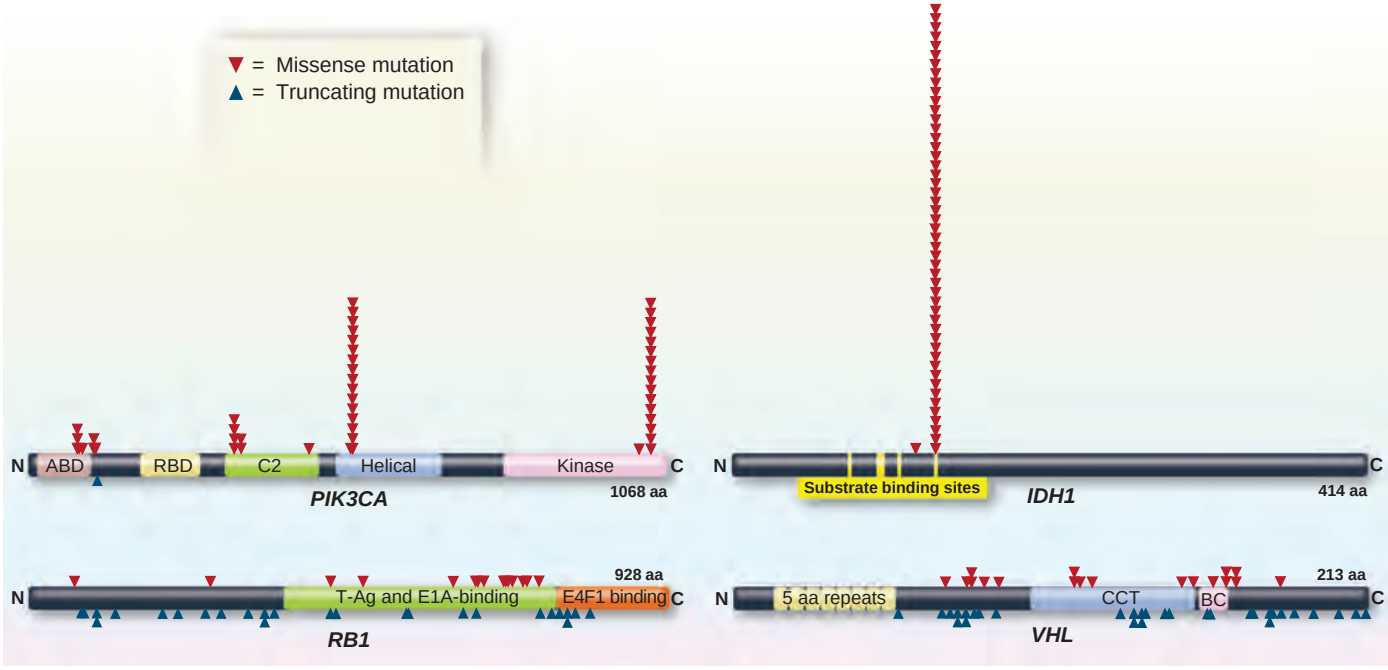

Fig. 4. Distribution of mutations in two oncogenes (*PIK3CA* and *IDH1*) and two tumor suppressor genes (*RB1* and *VHL*). The distribution of missense mutations (red arrowheads) and truncating mutations (blue arrowheads) in representative oncogenes and tumor suppressor genes are shown. The data were collected from genome-wide studies annotated in the COSMIC database (release version 61). For *PIK3CA* and *IDH1*, mutations obtained from the COSMIC database were randomized by the Excel RAND function, and the first 50 are shown. For *RB1* and *VHL*, all mutations recorded in COSMIC are plotted. aa, amino acids.

regions of the genome in an apparently random fashion (*28*). Thus, at best, methods based on mutation frequency can only prioritize genes for further analysis but cannot unambiguously identify driver genes that are mutated at relatively low frequencies.

Further complicating matters, there are two distinct meanings of the term "driver gene" that are used in the cancer literature. The driver-versus-passenger concept was originally used to distinguish mutations that caused a selective growth advantage from those that did not (*29*). According to this definition, a gene that does not harbor driver gene mutations cannot be a driver gene. But many genes that contain few or no driver gene mutations have been labeled driver genes in the literature. These include genes that are overexpressed, underexpressed, or epigenetically altered in tumors, or those that enhance or inhibit some aspect of tumorigenicity when their expression is experimentally manipulated. Though a subset of these genes may indeed play an important role in the neoplastic process, it is confusing to lump them all together as driver genes.

To reconcile the two connotations of driver genes, we suggest that genes suspected of increasing the selective growth advantage of tumor cells be categorized as either "Mut-driver genes" or "Epi-driver genes." Mut-driver genes contain a sufficient number or type of driver gene mutations to unambiguously distinguish them from other genes. Epi-driver genes are expressed aberrantly in tumors but not frequently mutated; they are altered through changes in DNA methylation or chromatin modification that persist as the tumor cell divides.

A Ratiometric Method to Identify and Classify Mut-Driver Genes

If mutation frequency, corrected for mutation context, gene length, and other parameters, cannot reliably identify modestly mutated driver genes, what can? In our experience, the best way to identify Mut-driver genes is through their pattern of mutation rather than through their mutation frequency. The patterns of mutations in well-studied oncogenes and tumor suppressor genes are highly characteristic and nonrandom. Oncogenes are recurrently mutated at the same amino acid positions, whereas tumor suppressor genes are mutated through protein-truncating alterations throughout their length (Fig. 4 and table S2A).

On the basis of these mutation patterns rather than frequencies, we can determine which of the 18,306 mutated genes containing a total of 404,863 subtle mutations that have been recorded in the Catalogue of Somatic Mutations in Cancer (COSMIC) database (*30*) are Mut-driver genes and whether they are likely to function as oncogenes or tumor suppressor genes. To be classified as an oncogene, we simply require that >20% of the recorded mutations in the gene are at recurrent positions and are missense (see legend to table S2A). To be classified as a tumor suppressor gene, we analogously require that >20% of the recorded mutations in the gene are inactivating. This "20/20 rule" is lenient in that all well-documented cancer genes far surpass these criteria (table S2A).

The following examples illustrate the value of the 20/20 rule. When *IDH1* mutations were first identified in brain tumors, their role in tumorigenesis was unknown (*2*, *31*). Initial functional studies suggested that *IDH1* was a tumor suppressor gene and that mutations inactivated this gene (*32*). However, nearly all of the mutations in *IDH1* were at the identical amino acid, codon 132 (Fig. 4). As assessed by the 20/20 rule, this distribution unambiguously indicated that *IDH1* was an oncogene rather than a tumor suppressor gene, and this conclusion was eventually supported by biochemical experiments (*33*, *34*). Another example is provided by mutations in *NOTCH1*. In this case, some functional studies suggested that *NOTCH1* was an oncogene, whereas others suggested it was a tumor suppressor gene (*35*, *36*). The situation could be clarified through the application of the 20/20 rule to *NOTCH1* mutations in cancers. In "liquid tumors" such as lymphomas and leukemias, the mutations were often recurrent and did not truncate the predicted protein (*37*). In squamous cell carcinomas, the mutations were not recurrent and were usually inactivating (*38*–*40*). Thus, the genetic data clearly indicated that *NOTCH1* functions differently in different tumor types. The idea that the same gene can function

in completely opposite ways in different cell types is important for understanding cell signaling pathways.

How Many Mut-Driver Genes Exist?

Though all 20,000 protein-coding genes have been evaluated in the genome-wide sequencing studies of 3284 tumors, with a total of 294,881 mutations reported, only 125 Mut-driver genes, as defined by the 20/20 rule, have been discovered to date (table S2A). Of these, 71 are tumor suppressor genes and 54 are oncogenes. An important but relatively small fraction (29%) of these genes was discovered to be mutated through unbiased genome-wide sequencing; most of these genes had already been identified by previous, more directed investigations.

How many more Mut-driver genes are yet to be discovered? We believe that a plateau is being reached, because the same Mut-driver genes keep being "rediscovered" in different tumor types. For example, *MLL2* and *MLL3* mutations were originally discovered in medulloblastomas (*41*) and were subsequently discovered to be mutated in non-Hodgkin lymphomas, prostate cancers, breast cancers, and other tumor types (*42*–*45*). Similarly, *ARID1A* mutations were first discovered to be mutated in clear-cell ovarian cancers (*46*, *47*) and were subsequently shown to be mutated in tumors of several other organs, including those of the stomach and liver (*48*–*50*). In recent studies of several types of lung cancer (*4*, *51*, *52*), nearly all genes found to be mutated at significant frequencies had already been identified in tumors of other organs. In other words, the number of frequently altered Mut-driver genes (mountains) is nearing saturation. More mountains will undoubtedly be discovered, but these will likely be in uncommon tumor types that have not yet been studied in depth.

The newly discovered Mut-driver genes that have been detected through genome-wide sequencing have often proved illuminating. For example, nearly half of these genes encode proteins that directly regulate chromatin through modification of histones or DNA. Examples include the histones HIST1H3B and H3F3A, as well as the proteins DNMT1 and TET1, which covalently modify DNA, EZH2, SETD2, and KDM6A, which, in turn, methylate or demethylate histones (*53*–*57*). These discoveries have profound implications for understanding the mechanistic basis of the epigenetic changes that are rampant in tumors (*58*). The discovery of genetic alterations in genes encoding mRNA splicing factors, such as *SF3B1* and *U2AF1* (*59*–*61*), was similarly stunning, as mutations in these genes would be expected to lead to a plethora of nonspecific cellular stresses rather than to promote specific tumor types. Another example is provided by mutations in the cooperating proteins ATRX and DAXX (*62*). Tumors with mutations in these genes all have a specific type of telomere elongation process termed "ALT" (for "alternative lengthening of telomeres") (*63*). Though the ALT phenotype had been recognized for more than a decade, its genetic basis was mysterious before the discovery of mutations of these genes and their perfect correlation with the ALT phenotype (*64*). A final example is provided by *IDH1* and *IDH2*, whose mutations have stimulated the burgeoning field of tumor metabolism (*65*) and have had fascinating implications for epigenetics (*66*, *67*).

The Mut-driver genes listed in table S2A are affected by subtle mutations: base substitutions, intragenic insertions, or deletions. As noted above, Mut-driver genes can also be altered by less subtle changes, such as translocations, amplifications, and large-scale deletions. As with point mutations, it can be difficult to distinguish Mut-driver genes that are altered by these types of changes from genes that contain only passenger mutations. Genes that are not point-mutated, but are recurrently amplified (e.g., *MYC* family genes) or homozygously deleted (e.g., *MAP2K4*) and that meet other criteria (e.g., being the only gene in the amplicon or homozygously deleted region) are listed in table S2B. This adds 13 Mut-driver genes—10 oncogenes that are amplified and 3 tumor suppressor genes that are homozygously deleted—to the 125 driver genes that are affected by subtle mutations, for a total of 138 driver genes discovered to date (table S2).

Translocations provide similar challenges for driver classification. An important discovery related to this point is chromothripsis (*68*), a rare cataclysmic event involving one or a small number of chromosomes that results in a large number of chromosomal rearrangements. This complicates any inferences about causality, in the same way that mismatch repair deficiency compromises the interpretation of point mutations. However, for completeness, all fusion genes that have been identified in at least three independent tumors are listed in table S3. Virtually all of these genes were discovered through conventional approaches before the advent of genome-wide DNA sequencing studies, with some notable exceptions such as those described in (*6*) and (*69*). The great majority of these translocations are found in liquid tumors (leukemias and lymphomas) (table S3C) or mesenchymal tumors (table S3B) and were initially identified through karyotypic analyses. A relatively small number of recurrent fusions, the most important of which include *ERG* in prostate cancers (*70*) and *ALK* in lung cancers (*71*), have been described in more common tumors (table S3A).

Genes exist that predispose to cancer when inherited in mutant form in the germ line, but are not

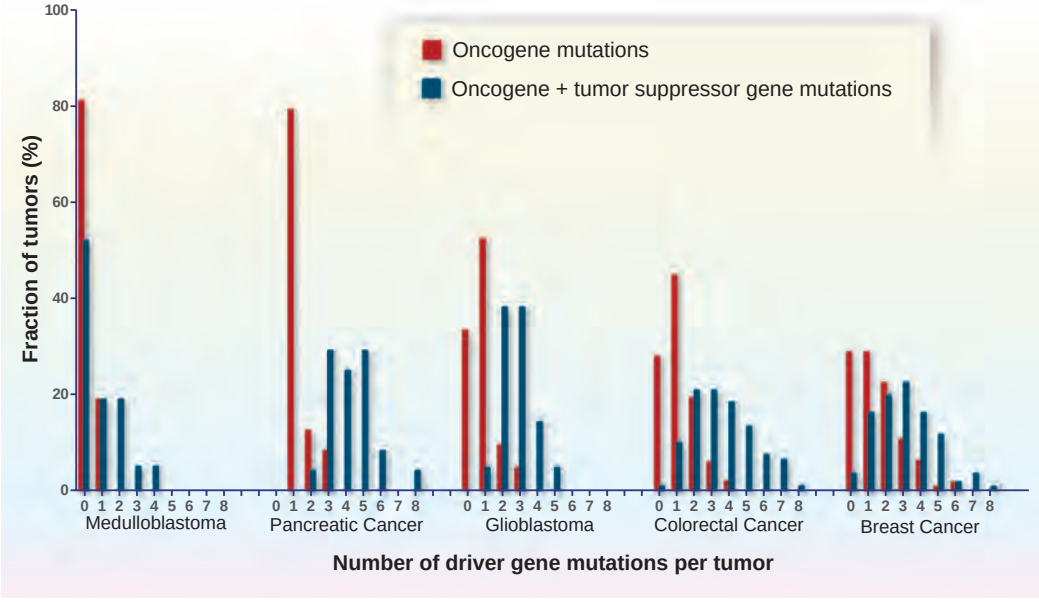

Fig. 5. Number and distribution of driver gene mutations in five tumor types. The total number of driver gene mutations [in oncogenes and tumor suppressor genes (TSGs)] is shown, as well as the number of oncogene mutations alone. The driver genes are listed in tables S2A and S2B. Translocations are not included in this figure, because few studies report translocations along with the other types of genetic alterations on a per-case basis. In the tumor types shown here, translocations affecting driver genes occur in less than 10% of samples. The published data on which this figure is based are provided in table S1E.

somatically mutated in cancer to a substantial degree. These genes generally do not confer an increase in selective growth advantage when they are abnormal, but they stimulate tumorigenesis in indirect ways (such as by increasing genetic instability, as discussed later in this Review). For completeness, these genes and the hereditary syndromes for which they are responsible are listed in table S4.

Dark Matter

Classic epidemiologic studies have suggested that solid tumors ordinarily require five to eight "hits," now interpreted as alterations in driver genes, to develop (*72*). Is this number compatible with the molecular genetic data? In pediatric tumors such as medulloblastomas, the number of driver gene mutations is low (zero to two), as expected from the discussion above (Fig. 5). In common adult tumors—such as pancreatic, colorectal, breast, and brain cancers—the number of mutated driver genes is often three to six, but several tumors have only one or two driver gene mutations (Fig. 5). How can this be explained, given the widely accepted notion that tumor development and progression require multiple, sequential genetic alterations acquired over decades?

First, technical issues explain some of the "missing mutations." Genome-wide sequencing is far from perfect, at least with the technologies available today. Some regions of the genome are not well represented because their sequences are difficult to amplify, capture, or unambiguously map to the genome (*73*–*76*). Second, there is usually a wide distribution in the number of times that a specific nucleotide in a given gene is observed in the sequence data, so some regions will not be well represented by chance factors alone (*77*). Finally, primary tumors contain not only neoplastic cells, but also stromal cells that dilute the signal from the mutated base, further reducing the probability of finding a mutation (*78*).

What fraction of mutations are missed by these three technical issues? A recent study of pancreatic cancers is informative in this regard. Biankin *et al*. used immunohistochemical and genetic analyses to select a set of primary tumor samples enriched in neoplastic cells (*79*). They used massively parallel sequencing to analyze the exomes of these samples, then compared their mutational data with a set of pancreatic cancer cell lines and xenografts in which mutations had previously been identified, using conventional Sanger sequencing, and confirmed to be present in the primary tumors (*3*, *16*). Only 159 (63%) of the expected 251 driver gene mutations were identified in the primary tumors studied by next-generation sequencing alone, indicating a false-negative rate of 37%. Genome-wide studies in which the proportion of neoplastic cells within tumors is not as carefully evaluated as in (*79*) will have higher false-negative rates. Moreover, these technical problems are exacerbated in whole-genome studies compared with exomic analyses, because the sequence coverage of the former is often lower than that of the latter (generally 30-fold in whole-genome studies versus more than 100-fold in exomic studies).

Conceptual issues also limit the number of detectable drivers. Virtually all studies, either at the whole-genome or whole-exome level, have focused on the coding regions. The reason for this is practical; it is difficult enough to identify driver gene mutations when they qualitatively alter the sequence of the encoded protein. Trying to make sense of intergenic or intronic mutations is much more difficult. Based on analogous studies of the identifiable mutations in patients with monogenic diseases, more than 80% of mutations should be detectable through analysis of the coding regions (*80*). However, this still leaves some mutations as unidentifiable "dark matter," even in the germline genomes of heritable cases, which are usually easier to interpret than the somatic mutations in cancers. The first examples of light coming to such dark matter have recently been published: Recurrent mutations in the promoter of the *TERT* gene, encoding the catalytic subunit of telomerase, have been identified and shown to activate its transcription (*81*, *82*).

Mut-driver genes other than those listed in table S2 will undoubtedly be discovered as genome-wide sequencing continues. However, based on the trends noted above, most of the Mut-driver genes will likely be mountains in rare tumor types or small hills in common tumor types; thus, these genes are unlikely to account for the bulk of the presumptive dark matter. Other types of dark matter can be envisioned, however. Copy-number alterations are ubiquitous in cancers, at either the whole-chromosome or subchromosomal levels. These alterations could subtly change the expression of their driver genes. Recent studies have suggested that the loss of one copy of chromosomes containing several tumor suppressor genes, each plausibly connected to neoplasia but not altered by

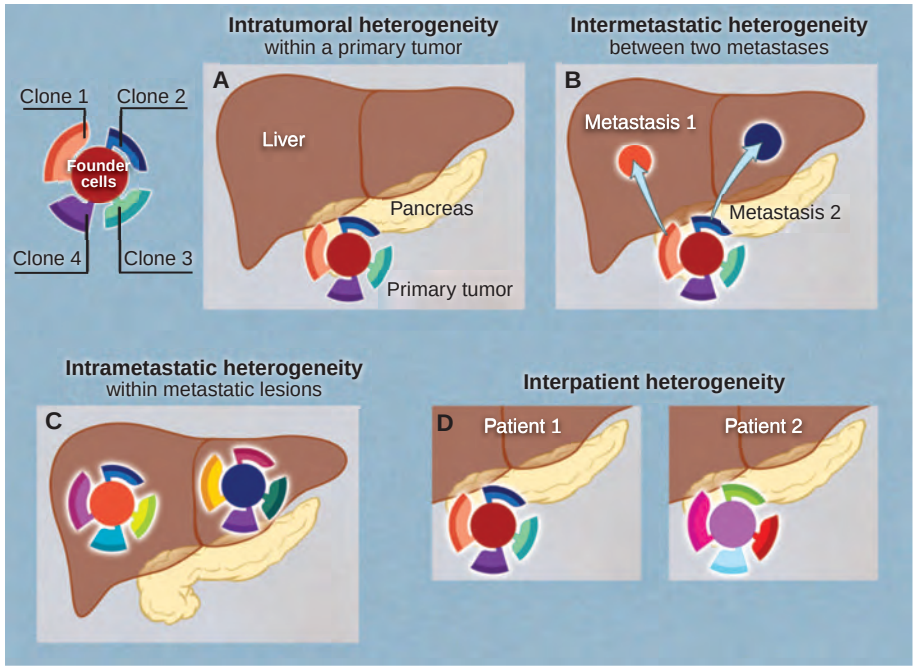

Fig. 6. Four types of genetic heterogeneity in tumors, illustrated by a primary tumor in the pancreas and its metastatic lesions in the liver. Mutations introduced during primary tumor cell growth result in clonal heterogeneity. At the top left, a typical tumor is represented by cells with a large fraction of the total mutations (founder cells) from which subclones are derived. The differently colored regions in the subclones represent stages of evolution within a subclone. (**A**) Intratumoral: heterogeneity among the cells of the primary tumor. (**B**) Intermetastatic: heterogeneity among different metastatic lesions in the same patient. In the case illustrated here, each metastasis was derived from a different subclone. (**C**) Intrametastatic: heterogeneity among the cells of each metastasis develops as the metastases grow. (**D**) Interpatient: heterogeneity among the tumors of different patients. The mutations in the founder cells of the tumors of these two patients are almost completely distinct (see text).

CREDIT: FIG. 6, E. COOK

mutation, may confer a selective growth advantage (*83*, *84*).

The most obvious source of dark matter is in Epi-driver genes. Human tumors contain large numbers of epigenetic changes affecting DNA or chromatin proteins. For example, a recent study of colorectal cancers showed that more than 10% of the protein-coding genes were differentially methylated when compared with normal colorectal epithelial cells (*85*). Some of these changes (i.e., those in Epi-driver genes) are likely to provide a selective growth advantage (*86*, *87*). For example, epigenetic silencing of *CDK2NA* and *MLH1* is much more common than mutational inactivation of either of these two well-recognized driver genes (*85*) However, there is a critical difference between a genetic and an epigenetic change in a gene. Unlike the sequence of a gene in a given individual, methylation is plastic, varying with cell type, developmental stage, and patient age (*21*). The methylation state of the normal precursor cells that initiate tumorigenesis is unknown; these cells, such as normal stem cells, may represent only a tiny fraction of the cells in a normal organ. This plasticity also means that methylation can change under microenvironmental cues, such as those associated with low nutrient concentrations or abnormal cell contacts. It is therefore difficult to know whether specific epigenetic changes observed in cancer cells reflect, rather than contribute to, the neoplastic state. Criteria for distinguishing epigenetic changes that exert a selective growth advantage from those that do not (passenger epigenetic changes) have not yet been formulated. Given that Epi-driver genes are likely to compose a major component of the dark matter, further research on this topic is essential (*58*).

Genetic Heterogeneity

The mutations depicted in Fig. 1 are clonal; that is, they are present in the majority of the neoplastic cells in the tumors. But additional, subclonal (i.e., heterogeneous within the tumor) mutations are important for understanding tumor evolution. Four types of genetic heterogeneity are relevant to tumorigenesis (Fig. 6):

1) Intratumoral: heterogeneity among the cells of one tumor. This type of heterogeneity has been recognized for decades. For example, it is rare to see a cytogenetic study of a solid tumor in which all of the tumor cells display the same karyotype (*88*). The same phenomenon has been noted for individual genes [e.g., (*89*)] and more recently has been observed throughout the genome (*16*, *90*–*96*). This kind of heterogeneity must exist: Every time a normal (or tumor) cell divides, it acquires a few mutations, and the number of mutations that distinguish any two cells simply marks the time from their last common ancestor (their founder cell). Cells at the opposite ends of large tumors will be spatially distinct and, in general, will display more differences than neighboring cells (*16*). This phenomenon is analogous to speciation, wherein organisms on different islands are more likely to diverge from one another than are organisms on the same island.

In studies that have evaluated intratumoral heterogeneity by genome-wide sequencing, the majority of somatic mutations are present in all tumor cells. These mutations form the trunk of the somatic evolutionary tree. What is the importance of the mutations in the branches (i.e., those that are not shared by all tumor cells)? From a medical perspective, these mutations are often meaningless because the primary tumors are surgically removed. How much heterogeneity existed in the various branches before surgery is not important. However, this heterogeneity provides the seeds for intermetastastic heterogeneity, which is of great clinical importance.

2) Intermetastatic: heterogeneity among different metastatic lesions of the same patient. The vast majority of cancer patients die because their tumors were not removed before metastasis to surgically inaccessible sites, such as the liver, brain, lung, or bone. Patients who relapse with a single metastatic lesion can often still be cured by surgery or radiotherapy, but single metastases are the exception rather than the rule. A typical patient on a clinical trial has a dozen or more metastatic lesions large enough to be visualized by imaging, and many more that are smaller. If each of the metastatic lesions in a single patient was founded by a cell with a very different genetic constitution, then chemotherapeutic cures would be nearly impossible to achieve: Eradicating a subset of the metastatic lesions in a patient will not be adequate for long-term survival.

How much heterogeneity is there among different metastatic lesions? In short, a lot. It is not uncommon for one metastatic lesion to have 20 clonal genetic alterations not shared by other metastases in the same patient (*16*, *97*). Because they are clonal, these mutations occurred in the founder cell of the metastasis; that is, the cell that escaped from the primary tumor and multiplied to form the metastasis. The founder cell for each metastasis is present in different, geographically distinct areas of the primary tumors, as expected (*16*).

This potentially disastrous situation is tempered by the fact that the heterogeneity appears largely confined to passenger gene mutations. In most of the studies documenting heterogeneity in malignancies, the Mut-driver genes are present in the trunks of the trees, though exceptions have been noted (*95*). These findings are consistent with the idea, discussed above, that the genetic alterations required for metastasis were present (i.e., selected for) before metastasis actually occurred. The data are also consistent with the observation that in patients responsive to targeted agents, the response is often seen in all metastatic lesions rather than just a small subset (*98*).

3) Intrametastatic: heterogeneity among the cells of an individual metastasis. Each metastasis is established by a single cell (or small group of cells) with a set of founder mutations. As it grows, the metastasis acquires new mutations with each cell division. Though the founder mutations may make the lesion susceptible to antitumor agents, the new mutations provide the seeds for drug resistance. Unlike primary tumors, the metastatic lesions generally cannot be removed by surgery and must be treated with systemic therapies. Patients with complete responses to targeted therapies invariably relapse. Most of the initial lesions generally recur, and the time frame at which they recur is notably similar. This time course can be explained by the presence of resistance mutations that existed within each metastasis before the onset of the targeted therapy (*99*–*102*). Calculations show that any metastatic lesion of a size visible on medical imaging has thousands of cells (among the billions present) that are already resistant to virtually any drug that can be imagined (*99*, *101*, *102*). Thus, recurrence is simply a matter of time, entirely predictable on the basis of known mutation frequencies and tumor cell growth rates. This "fait accompli" can be circumvented, in principle, by treatment with multiple agents, as it is unlikely that a single tumor cell will be resistant to multiple drugs that act on different targets.

4) Interpatient: heterogeneity among the tumors of different patients. This type of heterogeneity has been observed by every oncologist; no two cancer patients have identical clinical courses, with or without therapy. Some of these differences could be related to host factors, such as germline variants that determine drug half-life or vascular permeability to drugs or cells, and some could be related to nongenetic factors (*103*). However, much of this interpatient heterogeneity is probably related to somatic mutations within tumors. Though several dozen somatic mutations may be present in the breast cancers from two patients, only a small number are in the same genes, and in the vast majority of cases, these are the Mut-driver genes (*1*, *104*, *105*). Even in these driver genes, the actual mutations are often different. Mutations altering different domains of a protein would certainly not be expected to have identical effects on cellular properties, as experimentally confirmed (*106*). Though it may seem that different mutations in adjacent codons would have identical effects, detailed studies of large numbers of patients have shown that this need not be the case. For example, a $Gly^{12} \rightarrow Asp^{12}$ (G12D) mutation of *KRAS* does not have the same clinical implications as a G13D mutation of the same gene (*107*). Interpatient heterogeneity has always been one of the major obstacles

to designing uniformly effective treatments for cancer. Efforts to individualize treatments based on knowledge of the genomes of cancer patients are largely based on an appreciation of this heterogeneity.

Signaling Pathways in Tumors

The immense complexity of cancer genomes that could be inferred from the data described above is somewhat misleading. After all, even advanced tumors are not completely out of control, as evidenced by the dramatic responses to agents that target mutant *BRAF* in melanomas (*108*) or mutant *ALK* in lung cancers (*109*). Albeit transient, these responses mean that interference with even a single mutant gene product is sufficient to stop cancer in its tracks, at least transiently. How can the genomic complexity of cancer be reconciled with these clinical observations?

Two concepts bear on this point. The first, mentioned above, is that >99.9% of the alterations in tumors (including point mutations, copy-number alterations, translocations, and epigenetic changes distributed throughout the genome, not just in the coding regions) are immaterial to neoplasia. They are simply passenger changes that mark the time that has elapsed between successive clonal expansions. Normal cells also undergo genetic alterations as they divide, both at the nucleotide and chromosomal levels. However, normal cells are programmed to undergo cell death in response to such alterations, perhaps as a protective mechanism against cancer. In contrast, cancer cells have evolved to tolerate genome complexity by acquiring mutations in genes such as *TP53* (*110*). Thus, genomic complexity is, in part, the result of cancer, rather than the cause.

To appreciate the second concept, one must take the 30,000-foot view. A jungle might look chaotic at ground level, but the aerial view shows a clear order, with all the animals gathering at the streams at certain points in the day, and all the streams converging at a river. There is order in cancer, too. Mutations in all of the 138 driver genes listed in table S2 do one thing: cause a selective growth advantage, either directly or indirectly. Moreover, there appears to be only a limited number of cellular signaling pathways through which a growth advantage can be incurred (Fig. 7 and table S5).

All of the known driver genes can be classified into one or more of 12 pathways (Fig. 7). The discovery of the molecular components of these pathways is one of the greatest achievements of biomedical research, a tribute to investigators working in fields that encompass biochemistry, cell biology, and development, as well as cancer. These pathways can themselves be further organized into three core cellular processes:

1) Cell fate: Numerous studies have demonstrated the opposing relationship between cell division and differentiation, the arbiters of cell fate. Dividing cells that are responsible for populating normal tissues (stem cells) do not differentiate, and vice versa. Regenerative medicine is based on this distinction, predicated on ways to get differentiated cells to dedifferentiate into stem cells, then forcing the stem cells to differentiate into useful cell types for transplantation back into the patient. Many of the genetic alterations in cancer abrogate the precise balance between differentiation and division, favoring the latter. This causes a selective growth advantage, because differentiating cells eventually die or become quiescent. Pathways that function through this process include APC, HH, and NOTCH, all of which are well known to control cell fate in organisms ranging from worms to mammals (*111*). Genes encoding chromatin-modifying enzymes can also be included in this category. In normal development, the heritable switch from division to differentiation is not determined by mutation, as it is in cancer, but rather by epigenetic alterations affecting DNA and chromatin proteins. What better way to subvert this normal mechanism for controlling tissue architecture than to debilitate the epigenetic modifying apparatus itself?

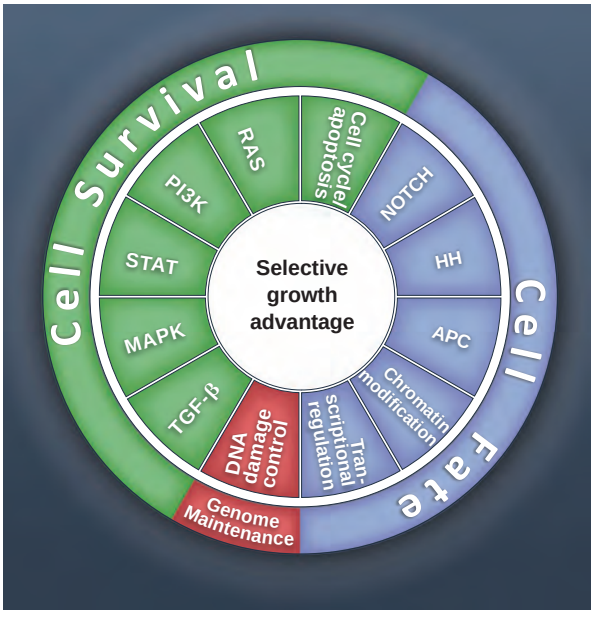

Fig. 7. Cancer cell signaling pathways and the cellular processes they regulate. All of the driver genes listed in table S2 can be classified into one or more of 12 pathways (middle ring) that confer a selective growth advantage (inner circle; see main text). These pathways can themselves be further organized into three core cellular processes (outer ring). The publications on which this figure is based are provided in table S5.

2) Cell survival: Though cancer cells divide abnormally because of cell-autonomous alterations, such as those controlling cell fate, their surrounding stromal cells are perfectly normal and do not keep pace. The most obvious ramification of this asymmetry is the abnormal vasculature of tumors. As opposed to the well-ordered network of arteries, veins, and lymphatics that control nutrient concentrations in normal tissues, the vascular system in cancers is tortuous and lacks uniformity of structure (*112*, *113*). Normal cells are always within 100 μm of a capillary, but this is not true for cancer cells (*114*). As a result, a cancer cell acquiring a mutation that allows it to proliferate under limiting nutrient concentrations will have a selective growth advantage, thriving in environments in which its sister cells cannot. Mutations of this sort occur, for example, in the *EGFR*, *HER2*, *FGFR2*, *PDGFR*, *TGFβR2*, *MET*, *KIT*, *RAS*, *RAF*, *PIK3CA*, and *PTEN* genes (table S2A). Some of these genes encode receptors for the growth factors themselves, whereas others relay the signal from the growth factor to the interior of the cell, stimulating growth when activated (*115*, *116*). For instance, mutations in *KRAS* or *BRAF* genes confer on cancer cells the ability to grow in glucose concentrations that are lower than those required for the growth of normal cells or of cancer cells that do not have mutations in these genes (*117*, *118*). Progression through the cell cycle (and its antithesis, apoptosis) can be directly controlled by intracellular metabolites, and driver genes that directly regulate the cell cycle or apoptosis, such as *CDKN2A*, *MYC*, and *BCL2*, are often mutated in cancers. Another gene whose mutations enhance cell survival is *VHL*, the product of which stimulates angiogenesis through the secretion of vascular endothelial growth factor. What better way to provision growth factors to a rogue tumor than to lure the unsuspecting vasculature to its hideout?

3) Genome maintenance: As a result of the exotic microenvironments in which they reside, cancer cells are exposed to a variety of toxic substances, such as reactive oxygen species. Even without microenvironmental poisons, cells make mistakes while replicating their DNA or during division (*119*, *120*), and checkpoints exist to either slow down such cells or make them commit suicide (apoptosis) under such circumstances (*110*, *121*, *122*). Although it is good for the organism to remove these damaged cells, tumor cells that can survive the damage will, by definition, have a selective growth advantage. Therefore, it is not surprising that genes whose mutations abrogate these checkpoints, such as *TP53* and *ATM*, are mutated in cancers

(*123*). Defects in these genes can also indirectly confer a selective growth advantage by allowing cells that have a gross chromosomal change favoring growth, such as a translocation or an extra chromosome, to survive and divide. Analogously, genes that control point mutation rates, such as *MLH1* or *MSH2*, are mutated in cancers (table S2A) or in the germ line of patients predisposed to cancers (table S4) because they accelerate the acquisition of mutations that function through processes that regulate cell fate or survival. What better way to promote cancer than by increasing the rate of occurrence of the mutations that drive the process?

Because the protein products of genes regulating cell fate, cell survival, and genome maintenance often interact with one another, the pathways within them overlap; they are not as discrete as might be inferred from the description above. However, grouping genes into pathways makes perfect sense from a genetics standpoint. Given that cancer is a genetic disease, the principles of genetics should apply to its pathogenesis. When performing a conventional mutagenesis screen in bacteria, yeast, fruit flies, or worms, one expects to discover mutations in several different genes that confer similar phenotypes. The products of these genes often interact with one another and define a biochemical or developmental pathway. Therefore, it should not be surprising that several different genes can result in the same selective growth advantage for cancer cells and that the products of these genes interact. The analogy between cancer pathways and biochemical or developmental pathways in other organisms goes even deeper: The vast majority of our knowledge of the function of driver genes has been derived from the study of the pathways through which their homologs work in nonhuman organisms. Though the functions are not identical to those in human cells, they are highly related and have provided the starting point for analogous studies in human cells.

Recognition of these pathways also has important ramifications for our ability to understand interpatient heterogeneity. One lung cancer might have an activating mutation in a receptor for a stimulatory growth factor, making it able to grow in low concentrations of epidermal growth factor (EGF). A second lung cancer might have an activating mutation in *KRAS*, whose protein product normally transmits the signal from the epidermal growth factor receptor (EGFR) to other cell signaling molecules. A third lung cancer might have an inactivating mutation in *NF1*, a regulatory protein that normally inactivates the KRAS protein. Finally, a fourth lung cancer might have a mutation in *BRAF*, which transmits the signal from KRAS to downstream kinases (Fig. 8). One would predict that mutations in the various components of a single pathway would be mutually exclusive—that is, not occurring in the same tumor—and this has been experimentally confirmed (*124*, *125*). Apart from being intellectually satisfying, knowledge of these pathways has implications for cancer therapy, as discussed in the next section.

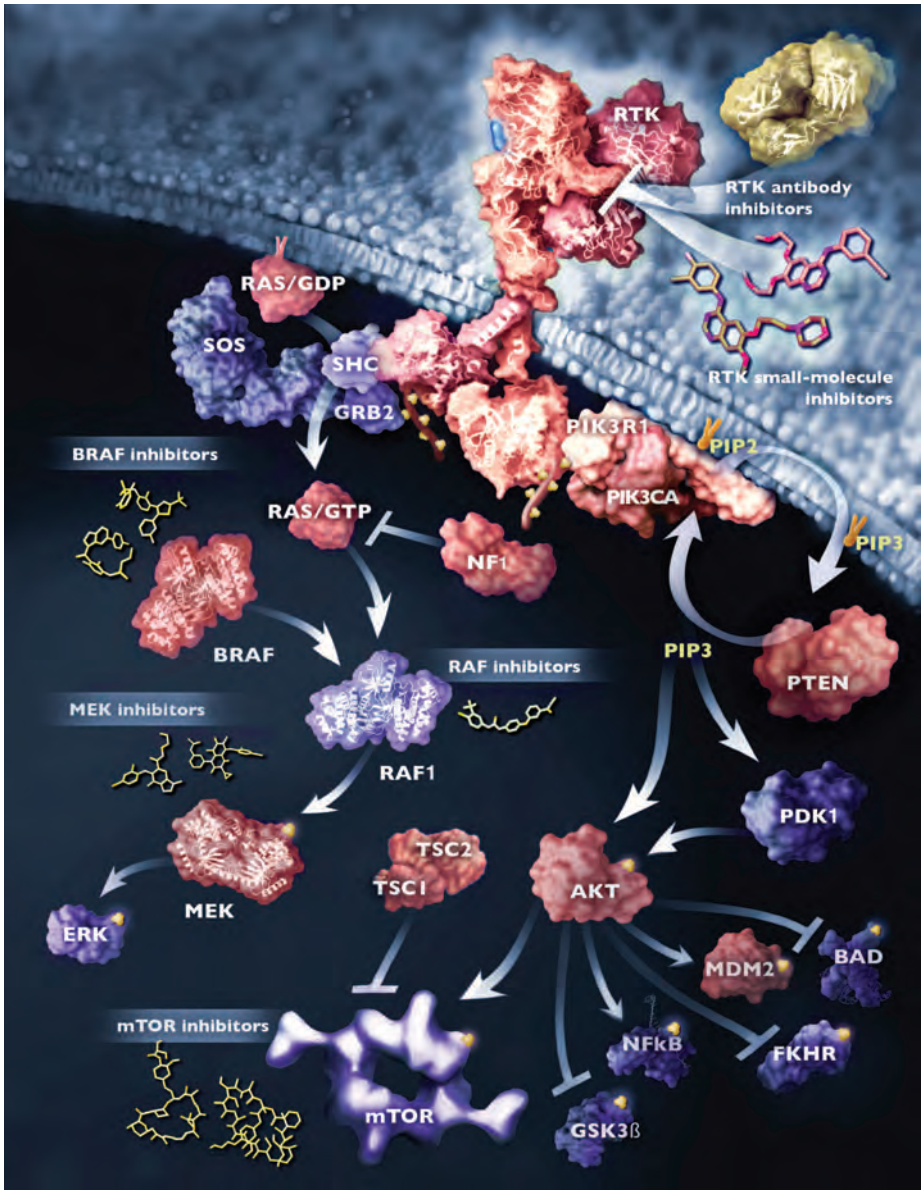

Fig. 8. Signal transduction pathways affected by mutations in human cancer. Two representative pathways from Fig. 7 (RAS and PI3K) are illustrated. The signal transducers are color coded: red indicates protein components encoded by the driver genes listed in table S2; yellow balls denote sites of phosphorylation. Examples of therapeutic agents that target some of the signal transducers are shown. RTK, receptor tyrosine kinase; GDP, guanosine diphosphate; MEK, MAPK kinase; ERK, extracellular signal–regulated kinase; NFkB, nuclear factor κB; mTOR, mammalian target of rapamycin.

CREDIT: FIG. 8, A. DIXON

A Perspective on Genome-Based Medicine in Oncology

Opportunities

Though cancer genome sequencing is a relatively new endeavor, it has already had an impact on the clinical care of cancer patients. The recognition that certain tumors contain activating mutations in driver genes encoding protein kinases has led to the development of small-molecule inhibitor drugs targeting those kinases.

Representative examples of this type of genome-based medicine include the use of EGFR kinase inhibitors to treat cancers with *EGFR* gene mutations (*126*), the aforementioned anaplastic lymphoma kinase (ALK) inhibitors to treat cancers with *ALK* gene translocations (*109*), and specific inhibitors of mutant BRAF

to treat cancers with *BRAF* mutations (*108*). Before instituting treatment with such agents, it is imperative to determine whether the cancer harbors the mutations that the drug targets. Only a small fraction of lung cancer patients have *EGFR* gene mutations or *ALK* gene translocations, and only these patients will respond to the drugs. Treating lung cancer patients without these particular genetic alterations would be detrimental, as such patients would develop the toxic side effects of the drugs while their tumors progressed.

A second type of genome-based medicine focuses on the side effects and metabolism of the therapeutic agents, rather than the genetic alterations they target. At present, the dose of cancer drugs given to patients is based on the patients' size (body weight or surface area). But the therapeutic ratio of cancer drugs (ratio of the concentration that causes side effects to the concentration required to kill tumor cells) is generally low, particularly for conventional (nontargeted) therapeutic agents. Small changes in circulating concentrations of these drugs can make the difference between substantial tumor regression and intolerable side effects. Interrogation of the germline status of the genes encoding drug-metabolizing enzymes could substantially improve the outcomes of treatment by informing drug dosing (*127*). Optimally, this genome interrogation would be accompanied by pharmacokinetic measurements of drug concentrations in each patient. The additional cost of such analyses would be small compared with the exorbitant costs of new cancer therapies—for recently approved drugs, the cost is estimated to be $200,000 to $300,000 per quality life year produced (*128*).

Challenges

One challenge of genome-based medicine in oncology is already apparent from the opportunities described above: All of the clinically approved drugs that target the products of genetically altered genes are directed against kinases. One reason for this is that kinases are relatively easy to target with small molecules and have been extensively studied at the biochemical, structural, and physiologic levels (*129*). But another reason has far deeper ramifications. The vast majority of drugs on the market today, for cancer or other diseases, inhibit the actions of their protein targets. This inhibition occurs because the drugs interfere with the protein's enzymatic activity (such as the phosphorylation catalyzed by kinases) or with the binding of the protein to a small ligand (such as with G protein–coupled receptors). Only 31 of the oncogenes listed in tables S2 and S3 have enzymatic activities that are targetable in this manner. Many others participate in protein complexes, involving large interfaces and numerous weak interactions. Inhibiting the function of such proteins with small drugs is notoriously difficult because small compounds can only inhibit one of these interactions (*130*, *131*).

Though one can at least imagine the development of drugs that inhibit nonenzymatic protein functions, the second challenge evident from table S2 poses even greater difficulties: A large fraction of the Mut-driver genes encode tumor suppressors. Drugs generally interfere with protein function; they cannot, in general, replace the function of defective genes such as those resulting from mutations in tumor suppressor genes. Unfortunately, tumor suppressor gene–inactivating mutations predominate over oncogene-activating mutations in the most common solid tumors: Few individual tumors contain more than one oncogene mutation (Fig. 5).

The relatively small number of oncogene mutations in tumors is important in light of the intrametastatic heterogeneity described earlier. To circumvent the inevitable development of resistance to targeted therapies, it will likely be necessary to treat patients with two or more drugs. The probability that a single cancer cell within a large metastatic lesion will be resistant to two agents that target two independent pathways is exponentially less than the probability that the cell will be resistant to a single agent. However, if the cancer cell does not contain more than one targetable genetic alteration (i.e., an oncogene mutation), then this combination strategy is not feasible.

Given the paucity of oncogene alterations in common solid tumors and these principles, can targeted therapeutic approaches ever be expected to induce long-term remissions, even cures, rather than the short-term remissions now being achieved? The saviors are pathways; every tumor suppressor gene inactivation is expected to result in the activation of some growth-promoting signal downstream of the pathway. An example is provided by *PTEN* mutations: Inactivation of the tumor suppressor gene *PTEN* results in activation of the AKT kinase (Fig. 8). Similarly, inactivation of the tumor suppressor gene *CDKN2A* results in activation of kinases, such as cyclin-dependent kinase 4, that promote cell cycle traverse (*132*). Furthermore, inactivation of tumor suppressor gene *APC* results in constitutive activity of oncogenes such as *CTNNB1* and *CMYC* (*133*–*135*).

We believe that greater knowledge of these pathways and the ways in which they function is the most pressing need in basic cancer research. Successful research on this topic should allow the development of agents that target, albeit indirectly, defective tumor suppressor genes. Indeed, there are already examples of such indirect targeting. Inactivating mutations of the tumor suppressor genes *BRCA1* or *BRCA2* lead to activation of downstream pathways required to repair DNA damage in the absence of BRCA function. Thus, cancer cells with defects in *BRCA1* or *BRCA2* are more susceptible to DNA damaging agents or to drugs that inhibit enzymes that facilitate the repair of DNA damage such as PARP [poly(adenosine diphosphate–ribose) polymerase] (*136*). PARP inhibitors have shown

Box 2. Highlights

1. Most human cancers are caused by two to eight sequential alterations that develop over the course of 20 to 30 years.

2. Each of these alterations directly or indirectly increases the ratio of cell birth to cell death; that is, each alteration causes a selective growth advantage to the cell in which it resides.

3. The evidence to date suggests that there are ~140 genes whose intragenic mutations contribute to cancer (so-called Mut-driver genes). There are probably other genes (Epi-driver genes) that are altered by epigenetic mechanisms and cause a selective growth advantage, but the definitive identification of these genes has been challenging.

4. The known driver genes function through a dozen signaling pathways that regulate three core cellular processes: cell fate determination, cell survival, and genome maintenance.

5. Every individual tumor, even of the same histopathologic subtype as another tumor, is distinct with respect to its genetic alterations, but the pathways affected in different tumors are similar.

6. Genetic heterogeneity among the cells of an individual tumor always exists and can impact the response to therapeutics.

7. In the future, the most appropriate management plan for a patient with cancer will be informed by an assessment of the components of the patient's germline genome and the genome of his or her tumor.

8. The information from cancer genome studies can also be exploited to improve methods for prevention and early detection of cancer, which will be essential to reduce cancer morbidity and mortality.

encouraging results in clinical trials when used in patients whose tumors have inactivating mutations of BRCA genes (*137*).

Further progress in this area will require more detailed information about the signaling pathways through which cancer genes function in human cancer cells, as well as in model organisms. One of the lessons of molecular biology over the past two decades is that pathway functions are different, depending on the organism, cell type, and precise genetic alterations in that cell (*138*). A pertinent example of this principle is provided by results of treatment with drugs inhibiting mutant BRAF kinase activity. In the majority of patients with melanomas harboring (V600E; V, Val; E, Glu) mutations in the *BRAF* gene, these drugs induce dramatic (though transient) remissions (*108*). But the same drugs have no therapeutic effect in colorectal cancer patients harboring the identical *BRAF* mutations (*139*). This observation has been attributed to the expression of EGFR, which occurs in some colorectal cancers but not in melanoma and is thought to circumvent the growth-inhibitory effects of the BRAF inhibitors. With this example in mind, no one should be surprised that a new drug that works well in an engineered tumor in mice fails in human trials; the organism is different, the cell type is usually different, and the precise genetic constitutions are always different. The converse of this statement—that a drug that fails in animal trials will not necessarily fail in human trials—has important practical consequences. In our view, if the biochemical and conceptual bases for a drug's actions are solid and the drug is shown to be safe in animals, then a human trial may be warranted, even if it does not shrink tumors in mice.

Genome-Based Medicines of the Future

Cancer genomes can also be exploited for the development of more effective immunotherapies. As noted above, typical solid tumors contain 30 to 70 mutations that alter the amino acid sequences of the proteins encoded by the affected genes. Each of these alterations is foreign to the immune system, as none have been encountered during embryonic or postnatal life. Therefore, these alterations, in principle, provide a "holy grail" for tumor immunology: truly tumor-specific antigens. These antigens could be incorporated into any of the numerous platforms that already exist for the immunotherapy of cancer. These include administration of vaccines containing the mutant peptide, viruses encoding the mutant peptides on their surfaces, dendritic cells presenting the mutated peptide, and antibodies or T cells with reactivity directed against the mutant peptides (*140*).

To realize these sorts of therapeutics, several conditions must be met. First, the mutant protein must be expressed. As cancer cells generally express about half of the proteins that are encoded by the human genome (*141*), this condition is not limiting. Second, as most proteins affected by mutations are intracellular, these mutations will not be visible to the immune system unless the mutant residue is presented in the context of a human leukocyte antigen (HLA) protein. Based on in silico analyses of binding affinities, it has been estimated that a typical breast or colorectal cancer contains 7 to 10 mutant proteins that can bind to an individual patient's HLA type (*142*). These theoretical predictions have recently gained experimental support. Studies of mouse tumors have identified mutant genes and shown that the corresponding peptides can induce antitumor immunity when administered as vaccines (*143*). Moreover, clinical trials of brain cancer patients immunized against a mutant peptide have yielded encouraging results (*144*).

As with all cancer therapies that are attractive in concept, obstacles abound in practice. If a tumor expresses a mutant protein that is recognizable as foreign, why has the host immune system not eradicated that tumor already? Indeed, immunoediting in cancers has been shown to exist, resulting in the down-regulation or absence of mutant epitopes that should have, and perhaps did, elicit an immune response during tumor development (*145*, *146*). Additionally, tumors can lose immunogenicity through a variety of genetic alterations, thereby precluding the presentation of epitopes that would otherwise be recognized as foreign (*147*). Though these theoretical limitations are disheartening, recent studies on immune regulation in humans portend cautious optimism (*148*, *149*).

Other Ways to Reduce Morbidity and Mortality Through Knowledge of Cancer Genomics

When we think about eradicating cancer, we generally think about curing advanced cases—those that cannot be cured by surgery alone because they have already metastasized. This is a curious way of thinking about this disease. When we think of cardiovascular or infectious diseases, we first consider ways to prevent them rather than drugs to cure their most advanced forms. Today, we are in no better position to cure polio or massive myocardial infarctions than we were a thousand years ago. But we can prevent these diseases entirely (vaccines), reduce incidence (dietary changes, statins), or mitigate severity (stents, thrombolytic agents) and thereby make a major impact on morbidity and mortality.

This focus on curing advanced cancers might have been reasonable 50 years ago, when the molecular pathogenesis of cancers was mysterious and when chemotherapeutic agents against advanced cancers were showing promise. But this mindset is no longer acceptable. We now know precisely what causes cancer: a sequential series of alterations in well-defined genes that alter the function of a limited number of pathways. Moreover, we know that this process takes decades to develop and that the incurable stage, metastasis, occurs only a few years before death. In other words, of the one million people that will die from cancer this year, the vast majority will die only because their cancers were not detected in the first 90% of the cancers' lifetimes, when they were amenable to the surgeons' scalpel.

This new knowledge of cancer (Box 2) has reinvigorated the search for cures for advanced cancers, but has not yet permeated other fields of applied cancer research. A common and limited set of driver genes and pathways is responsible for most common forms of cancer (table S2); these genes and pathways offer distinct potential for early diagnosis. The genes themselves, the proteins encoded by these genes, and the end products of their pathways are, in principle, detectable in many ways, including analyses of relevant body fluids, such as urine for genitourinary cancers, sputum for lung cancers, and stool for gastrointestinal cancers (*150*). Equally exciting are the possibilities afforded by molecular imaging, which not only indicate the presence of a cancer but also reveal its precise location and extent. Additionally, research into the relationship between particular environmental influences (diet and lifestyle) and the genetic alterations in cancer is sparse, despite its potential for preventative measures.

The reasons that society invests so much more in research on cures for advanced cancers than on prevention or early detection are complex. Economic issues play a part: New drugs are far more lucrative for industry than new tests, and large individual costs for treating patients with advanced disease have become acceptable, even in developing countries (*151*). From a technical standpoint, the development of new and improved methods for early detection and prevention will not be easy, but there is no reason to assume that it will be more difficult than the development of new therapies aimed at treating widely metastatic disease.

Our point is not that strenuous efforts to develop new therapies for advanced cancer patients should be abandoned. These will always be required, no matter our arsenal of early detection or preventative measures. Instead, we are suggesting that "plan A" should be prevention and early detection, and "plan B" (therapy for advanced cancers) should be necessary only when plan A fails. To make plan A viable, government and philanthropic organizations must dedicate a much greater fraction of their resources to this cause, with long-term considerations in mind. We believe that cancer deaths can be reduced by more than 75% in the coming decades (*152*), but that this reduction will only come about if greater efforts are made toward early detection and prevention.

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Acknowledgments: We thank M. Nowak and I. Bozic for critical reading of the manuscript, S. Gabelli for assisting with the production of Fig. 8, and A. Dixon, V. Ferranta, and E. Cook for artwork. This work was supported by The Virginia and D.K. Ludwig Fund for Cancer Research; The Lustgarten Foundation for Pancreatic Cancer Research; and NIH grants CA 43460, CA 47345, CA 62924, and CA 121113. All authors are Founding Scientific Advisors of Personal Genome Diagnostics (PGDx), a company focused on the identification of genetic alterations in human cancer for diagnostic and therapeutic purposes. All authors are also members of the Scientific Advisory Board of Inostics, a company that is developing technologies for the molecular diagnosis of cancer. All authors own stock in PGDx and Inostics. The terms of these arrangements are being managed by Johns Hopkins University, in accordance with their conflict-of-interest policies.

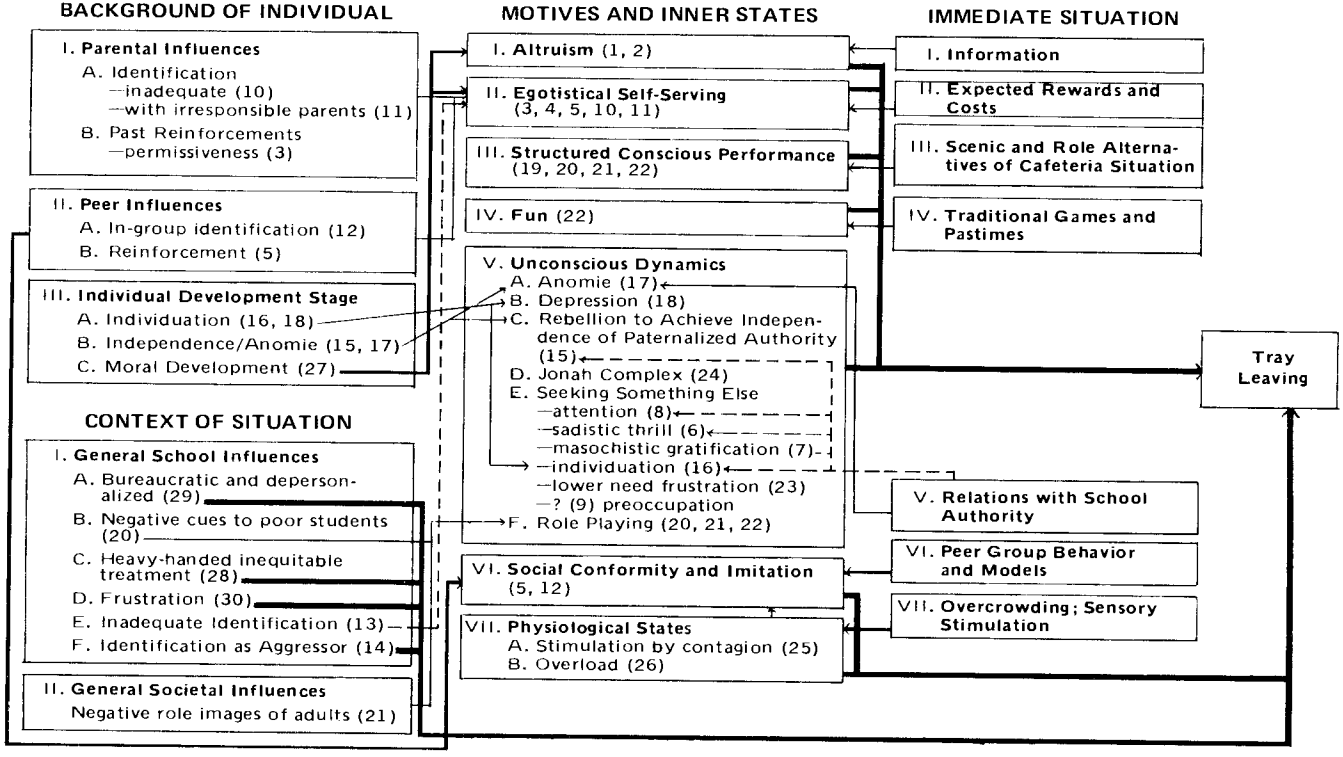
Supplementary Materials

www.sciencemag.org/cgi/content/full/339/6127/1546/DC1
Tables S1 to S5

10.1126/science.1235122

Figure 1.

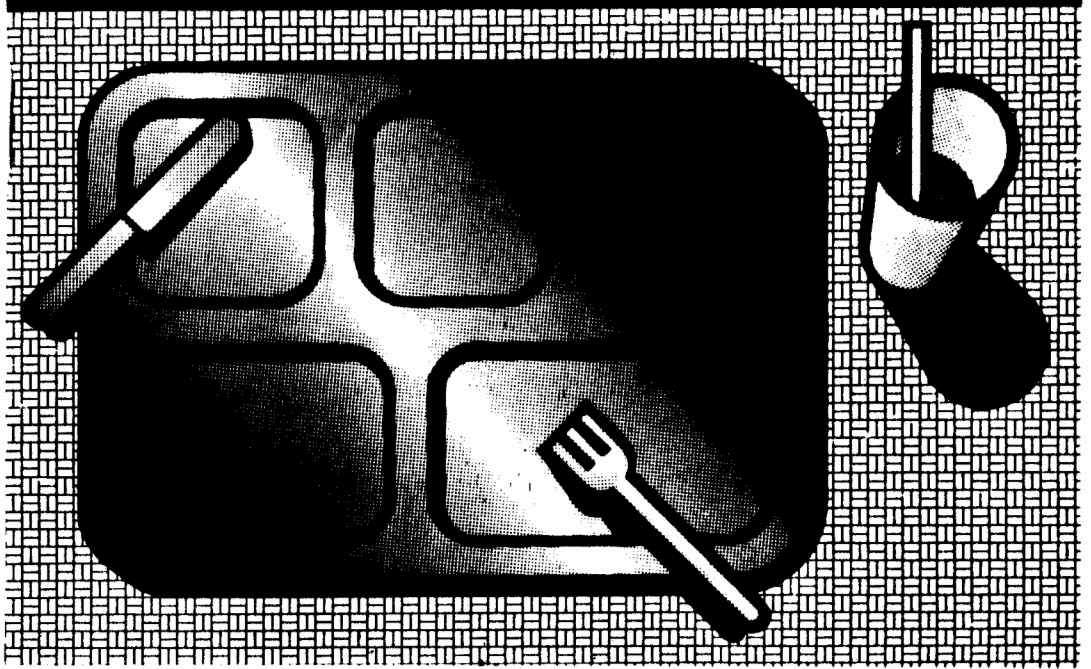
A MAP FOR THE ANALYSIS OF ONE INDIVIDUAL'S TRAY-LEAVING BEHAVIOR



The Case of the Unreturned Cafeteria Trays

An Investigation Based Upon Theories of Motivation and Human Behavior.

Lloyd S. Etheredge



THE CASE OF THE UNRETURNED CAFETERIA TRAYS

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The preparation of *The Case of the Unreturned Cafeteria Trays* was supported by Grant GY 9351 from the National Science Foundation to the American Political Science Association for a project to improve undergraduate education in political science. Sheilah R. Koeppen, Director of the Division of Educational Affairs, is the project director. Responsibility to the profession for the project activities, 1972-1975, is exercised by this Steering Committee on Undergraduate Education:

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This monograph has been commissioned by the Steering Committee on Undergraduate Education. It has been reviewed by three qualified persons, including a member of the Steering Committee. The monograph is published under the auspices of the Division of Educational Affairs. However, the views expressed are those of the contributors and not of the Steering Committee of the American Political Science Association.

ISBN 0-915654-16-4

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Foreword

Among the major activities of the American Political Science Association, the publication of the *American Political Science Review* and the Annual Meeting provide for exchange of information about research. Other major activities aim to adapt research to teaching needs, particularly at the undergraduate level.

Since the Association's establishment in 1904, there has always been a committee concerned with undergraduate education and, in each decade, an education committee has issued a report recommending instructional goals and strategies. Today, we have a different concept of useful educational activity; the Association is helping prepare instructional materials that can be utilized by teachers and students. The regional seminars for college teachers in the 1960s, supported by a grant from the Ford Foundation, were a notable first effort of this sort. The seminars helped teachers locate and use new sources of course materials and different methods of instruction. Several hundred political scientists participated in these seminars.

At the end of 1972, with the support of a grant from the National Science Foundation, the Association established a Division of Educational Affairs and began to develop publications providing teachers and students with instructional guides and useful materials. DEA NEWS for Teachers of Political Science, a newspaper received by all Association members; SETUPS, the student learning materials that introduce data analysis techniques and the Instructional Resource Monographs are the initial publications.

Each Instructional Resource Monograph is a guide to source materials or a method of instruction, and is designed primarily for faculty. The fifth monograph, *U.S. Census Data for Political and Social Research*, is accompanied by a manual for students. *The Case of the Unreturned Cafeteria Trays* is another student manual designed to facilitate faculty presentations of source material.

As political science selectively adapts theories and analytical techniques from other social sciences, it is appropriate that political science students learn theories of human behavior, from psychology, social psychology, sociology, and even economics. In *The Case of the Unreturned Cafeteria Trays* Lloyd Etheredge poses a problem and alternative solutions by way of engaging students in explorations of alternative interpretations of motivations. *The Case* includes readings and exercises for students to apply theories to analyze problems in political life.

Evron M. Kirkpatrick
Executive Director
American Political Science Association
June 1976

Acknowledgments

An early graduate seminar with Harold Lasswell helped to clarify and direct my developing interest in the policy science approach to improving American society. Teaching undergraduate courses in social and political psychology gave me the opportunity to develop the present monograph as a series of lectures. My colleagues Ken McVicar, Geoff Nelson, Jeffrey Pressman, Hayward Alker, and Martha Weinberg aided me with critical comments and useful advice. Eleanor Benson, Jacki Baizley, and Gail Lopata typed the manuscript.

Among the catalysts of this monograph was the pleasure, several years ago, when I read Robert K. Merton's *On the Shoulders of Giants: A Shandean Postscript*. More recently, Graham Allison's *Essence of Decision: Explaining the Cuban Missile Crisis* illustrated the benefits of explicating the images used in policy decision-making.

I want to express a personal debt of gratitude to the M.A.S.C. workshops and to their creator and first director, Felix Simon. The friendships and experiences during my eight years of association were deeply rewarding and were an important catalyst in my understanding of human behavior and the problems of effective leadership.

Finally I want to express my appreciation to the National Institute of Mental Health. Their fellowship support to me through Yale's Psychological Study of Politics program was instrumental in facilitating the interdisciplinary work that was an important part of my education. My thanks as well to Robert E. Lane and John B. McConahay, two men who helped to create and shape that program.

Introduction

Some people hope that "better human understanding" will eliminate coercion and inhumane practices in our world as well as alleviate a wide range of social problems: academic underachievement, use of hard drugs, drunken driving, alcoholism, crime, mental illness, sexism, racism, industrial pollution, and war are but a few examples where the hope has been expressed that better knowledge will help. Perhaps it will. But, if this is to come to pass, we must direct the knowledge of the social sciences toward fashioning better practical alternatives for the organization and conduct of our society.

I have chosen a simple problem to analyze in this way, an example from high school. It has seemed rather easy for my students to identify with the problem: high school is a shared experience in our society, and most high schools seem to have a cafeteria problem. But the analysis presented here is also a prototype of thinking that can be applied (with modifications and elaborations) to many of our social problems. This kind of thinking is, I would submit, useful: a more humane society will be simply the aggregate of all of us finding ways to be more humane and effective in our lives. Perhaps we can profit from stepping back and thinking about how to design institutions and create practices that make this possible.

Over ten years ago, when I was President of my high school Student Council, I was confronted with a problem in human behavior which I still find mysterious. I did not know what to do at the time and, as I have learned more about the complexities of human behavior and about the different theories and viewpoints for analyzing it, I still am not sure about the reasons for the problem, or what I, as a social scientist, would now recommend if I were called upon to give advice.

The situation was this: at my high school it had developed that some students who ate lunch in the cafeteria (almost all of the 2,200 students) were not taking back their trays to the dirty dish room but instead were departing for their classes leaving collections of trays, dirty dishes, and trash on the tables. Not all students were doing this—it was only a

minority. But, by the end of the lunch shifts (there were six of them), the cafeteria was a mess. And, as the principal pointed out when he called me to his office, it did take several man-hours of work by the cafeteria staff to make the place respectable again. Quite naturally, the cafeteria staff was angry and pressuring the principal to do something. And he wanted us (the Student Council) to do something.

Here, then, is our puzzle: what are the causes of this behavior? And what could be done to resolve the problem? The reader should be alerted that I now intend to illustrate a range of plausible answers to these questions by drawing systematically upon theories which social scientists use in thinking about behavior. This is, however, a theoretical paper: it does not solve the mystery of the unreturned cafeteria trays—that is a task for research. There will be no climax or grand finale. The characters and scenery along the way are all there is.

I. The Cybernetic Model

The cybernetic model imagines man as a goal-seeking animal who guides his behavior on the basis of information *feedback* from the environment. The notion of feedback can be illustrated by the example of a radar-controlled missile fired at a moving airplane: as the plane alters its course, radar impulses from the missile, bouncing off the plane, tell the missile how it should correct its flight so it will hit the target.[1]

It is possible, of course, to think of a variety of goals which a human being might try to achieve. For the sake of simplicity (and because the assumption is often made in applying cybernetic theory) let us assume that human beings would act laudably (return their trays) except for faulty feedback.

1. Ignorance of Expectations

The first explanation suggested by the cybernetic model is that students who do not return their trays might be ignorant of the expectations of the school. Perhaps they do not realize (because no one ever told them) that they should return their trays. Students would go along with the desires of the school administration if they knew what the expectations were, if the "lack of feedback" were corrected. The solution would be simple: tell them of the expectations.

2. "They Know Not What They Do" (Ignorance of Consequences)

A second and related explanation suggested by the cybernetic model is that students who do not return their trays might be unaware of the *consequences* of their behavior (the accumulated piles of trays, dishes, and trash at the end of the lunch shifts, the extra work for the cafeteria staff).

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[1] See Norbert Weiner (1962) *Cybernetics*, 2nd ed. Cambridge, New York: MIT Press and Wiley; and Karl Deutsch (1963) *The Nerves of Government: Models of Political Communication*, New York: Free Press of Glencoe.

If this explanation is correct, then the problem could be ended by a different policy choice—for example by taking classes on tours of the accumulated mess or by presenting the cafeteria manager to explain the situation over the public address system.

I have titled this second idea, "They Know Not What They Do," because the phrase is reminiscent of the last words of Christ on the cross: "Father, forgive them, for they know not what they do."[2] Cybernetic theories, as they are usually employed, are very *forgiving* theories. It is not something about individuals which should be blamed, rather it is something about the faulty information feedback mechanisms of their environment.

I should tell you that the cybernetic model was the one adopted by our student council. We did not believe the first hypothesis was true, that students were unaware of the school's expectations. But we were *hopeful* that, if they became aware of the problems caused by tray-leaving, most students would take back their trays.

I have stressed the word *hopeful* in the last sentence because I must confess that we were unsure that better feedback would be a cure. In part our advice was purely political: we did not want to be a "lackey" of the administration or have any role in policing other students. Yet we had to make some response to the principal's request for assistance if we were to maintain a good working relationship with him. The cybernetic model was a creative compromise to the pressures we were under. We would appear to be doing something without getting involved in coercion.[3] Then too, we were young, idealistic, and had an esthetic aversion to coercion.[4]

It might be useful to point out, in passing, that cybernetic theory does have a certain resonance with the assumptions of liberal political views, for example with the belief that people will act well if they are given enough education. Scientists and teachers generally, I think, have this kind of model in the back of their minds in justifying their work: they implicitly assume (as I do, in a way, in writing this monograph) that if people have better differentiated and more sophisticated "maps" of their social environment, if they know what effects are brought about by what causes, then they will act more humanely in the long run.

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[2]Luke 23:34.

[3]On the way in which such role conflicts can produce attitudes see, for example, F. X. Sutton et al., *The American Business Creed* (1956) Cambridge: Harvard University Press.

[4]On the place of esthetic sensibility in generating an aversion to coercion see Sigmund Freud (1933) "Why War?" *The Standard Edition of the Complete Psychological Works of Sigmund Freud*, vol. XXII, London: Hogarth Press, 203-215.

My high school principal, as you might guess, did not think well either of our recommendations based on cybernetic theory or of our faith in the good will of human nature. He was, centrally, a social learning theorist (by instinct, I think, rather than as a result of any knowledge of the experimental literature). Let me turn, then, to this behavior reinforcement model.

II. Social Learning

The social learning model imagines man as a hedonistic, reward-seeking punishment-avoiding animal. Behavior is the result of the rewards or punishments a man expects in the situation that confronts him, an expectation resulting partly from his past history of reinforcement (behavior which has been rewarded continues, behavior which has been punished decreases).[5] In research with animals it is usually assumed that food is a positive reinforcer if the animal is hungry, that electric shocks are punishment. It is more complex, in dealing with ordinary human behavior, to determine what will be a reward and what will be a punishment—but usually such things as money, praise, and social acceptance are thought to be rewards while economic costs or criticism from other people are punishments. The model suggests several explanations:

3. Too Permissive an Upbringing

Those students who do not return their trays come from homes where they always were rewarded whether they took their dishes back to the kitchen or not. The student tray-leavers, overly pampered and spoiled as children, were not properly conditioned.

4. "What's In It For Me?" (or) "Virtue Doesn't Pay"

Closely related to the preceding hypothesis is the hypothesis that those students who have not been "properly conditioned" also see a net cost in

[5]See for example Morton Deutsch and Robert Krauss (1965) *Theories in Social Psychology*, New York: Basic Books, chapter 4; Albert Bandura and R. H. Walters (1963) *Social Learning and Personality Development*, New York: Holt, Rinehart & Winston; B. F. Skinner (1948) *Walden Two*, New York: Macmillan, (1953) *Science and Human Behavior*, New York: Macmillan, (1971) *Beyond Freedom and Dignity*, New York: Knopf; George C. Homans (1974) *Social Behavior: Its Elementary Forms*, New York: Harcourt, Brace Jovanovich, rev. ed.; and Evelyn MacPherson et al. (1974) "A Comparison of Three Methods for Eliminating Disruptive Lunchroom Behavior," *Journal of Applied Behavior Analysis*, Vol. 7:2, 287-297.

taking their trays back: they are not paid to do it (it does take effort to walk to the other end of the cafeteria and stand in line for a minute or so). Some sages have argued that "virtue is its own reward" but these people are not going to be conned: to them, virtuous conduct requires more than the reward it provides.

My principal, very much a social learning theorist, decided the solution lay in increasing the costs to be incurred by wrongdoers. He adopted a random terror approach. Teacher monitors were placed in the cafeteria; these teachers were most annoyed at spending their lunch hours in a noisy, crowded cafeteria on monitor duty, and they let the students they caught know—in no uncertain terms—what socially objectionable persons they were for not returning their trays. In addition to this criticism, repeat offenders were also subject to the familiar repertoire of high school discipline (detention, suspension, parent conferences, etc.).

This attempted solution to the problem did have a modest effect in getting trays returned. It had this effect, however, at a certain cost—an increase in the irritability of teachers and a police state atmosphere in the cafeteria. The most important benefit, from the principal's point of view, was probably political and symbolic:[6] the cafeteria staff felt he was acting firmly, that he was "doing the best he could" in the situation. His seemingly decisive action made the cafeteria staff more willing to put up with clearing the remaining trays.

I think it would be unfair to behavior reinforcement theorists, however, to suggest that they would all endorse my principal's actions.[7] In general, behavior reinforcement research suggests that *rewards* may be more effective in changing behavior than punishments. But, even if my principal knew this, I think he would have chosen the punishment route because he simply had no rewards he could offer: certainly he had no money to pay students, and parents would not have accepted the solution of giving "good" students time off from school or higher grades. In fact I am at a loss, even now, to imagine what rewards a high school principal could give that his students would want: I do not picture the people I went to high

[6]Murray Edelman (1964) *The Symbolic Uses of Politics*, Urbana: University of Illinois Press.

[7]It is interesting to note, as an aside, that the broad application of behavior reinforcement principles in the classroom now seems to be well underway, albeit at a time when the cutting edge of research shows major problems with such applications. A recent review concludes: "The past 2 years have been bad ones for those of us who attempt to apply traditional principles of learning to instruction. Thorndike's principles of learning seem to be crumbling. . . . In fact, each one of the principles confidently enumerated by Skinner in *The Science of Learning and the Art of Teaching* now turns out to be untrue—at least in as general a sense as he believed at that time." Wilbert McKeachie (1974) "Instructional Psychology" in Mark Rosenzweig and Lyman Porter (eds.) *Annual Review of Psychology*, Vol. 25 Palo Alto: Annual Reviews, 161-193.

school with being highly motivated by the principal standing in the dirty dish room and praising them when they brought their trays back.

Perhaps my principal chose coercion only because he had no rewards. In fact, I think he also chose coercion because he was angry and because he *felt* that coercion would produce more change than rewards. (There now is some experimental evidence that individuals who use coercion to produce change *feel* more powerful than individuals who produce the same amount of change through rewards.[8]) Like many other people my principal seemed to believe implicitly that sticks were more effective than carrots.

I should add, I think, that my principal was conservative and probably felt a *moral obligation to society* to do something about the callous "what's in it for me" attitude he perceived. Conservatives and moralists often seem drawn toward coercion.[9,10] And a social learning theorist like my principal would tend to take tray-leaving more seriously, to view it as representing an attitude that would continue throughout life if it were not stopped.

It is interesting to note, in passing, that the discipline of economics is built upon the assumption of a "what's in it for me" calculation on the part of hedonistic individuals. The economists' perspective would suggest a rather elegant and simple solution to our problem—a market mechanism: all you need do is charge each student a 25¢ deposit on his tray when he buys his lunch. He receives the deposit back when he returns the tray. If he does not return the tray, he loses the deposit—*and* it becomes in the interest of other students to become entrepreneurs and cart it back.

[8]W. R. Kite (1964) "Attributions of Causality as a Function of the Use of Reward and Punishment" Unpublished Doctoral Dissertation, Stanford University; Barry R. Schlenker and James T. Tedeschi (1973) "Interpersonal Attraction and the Exercise of Coercive and Reward Power" *Human Relations* 26:5 427-439.

[9]Studies of American public education show that a strong conservative leaning is typical of its employees. See, for example, H. Ziegler, M. K. Jennings and G. W. Peaks (1974) "The Decision-Making Culture of American Public Education," in Cornelius P. Cotter (ed.) *Political Science Annual: An International Review,* Indianapolis: Bobbs-Merrill, Vol. 5, 177-226; also the evidence for high percentages of System 1 information processors in O. J. Harvey et al. "Teachers' Beliefs, Classroom Atmosphere and Student Behavior" (1972) reprinted in A. Morrison and D. McIntyre (eds.) *Social Psychology of Teaching,* Baltimore: Penguin Books, 215-229.

[10]It is of course not a common practice in our culture to reward people who act morally: the official version is that ethical conduct should be its own reward. However Montaigne in his *Essays* remarks that: "In China, a kingdom in which government and the arts, though they have had no contact with or knowledge of ours, contain examples that surpass them in many excellent features . . . the officers deputed by the prince to inspect the state of his provinces, when punishing those guilty of abusing their office, also reward, out of pure liberality, any whose conduct has been above the common level of honesty." M. E. Montaigne (1580) *Essays,* translated by J. M. Cohen (1958) Baltimore: Penguin Books.

I am not at all certain, however, that my principal would have found such a market system attractive even had he thought of it. As I said, he believed that there was a matter of morals at stake, a moral obligation toward other people. I think he would have been most reluctant to install any system which implied that one could legitimately ignore moral obligations by paying money.[11]

5. Small Group Rewards ("Evil Companions")

One elaboration of social learning theory would be to look at the groups to which individuals belong. Our research hypothesis would be that in some friendship groups there are *rewards* for leaving trays (e.g. appearing "tough," "courageous," or "independent"). This reference group notion is particularly interesting because it implies that individuals may be relatively insulated from direct influence by the administration. Moreover, it suggests that, for some reference groups, what the administration regards as punishment (e.g. detention) may actually be a reward, a kind of badge of courage, a source of respect and acceptance from other group members.[12] Perhaps breaking up such groups (by rotating lunch shift assignments) would work. Or you could attempt to exert peer group pressure through the student government.

[11]There are additional ethical problems in that such a market solution would favor rich kids—who presumably could better afford to "buy" the services of poorer kids. This kind of ethical problem is, of course, fundamental in the present use of an economic market system in American society.

[12]A useful discussion of such an approach in the light of juvenile delinquency research is Derek Wright (1971) *The Psychology of Moral Behavior,* Baltimore: Penguin Books; see also S. Glueck and E. Glueck (1966) "Varieties of Delinquent Types," *British Journal of Criminology,* Vol. 5, 236-248.

III. Psychoanalytic Theories

Both the cybernetic and the social learning perspectives are relatively well organized; hypotheses seem to flow in a straightforward way from the image of human behavior. This coherence is not characteristic of the psychoanalytic model. In fact about the only common element among psychoanalytic theories (when applied to a specific situation) is their tendency to emphasize unconscious dynamics and to use a specialized vocabulary. I have organized the following illustration of psychoanalytic theories in three categories: traditional theories which emphasize individual characteristics, traditional theories which emphasize a group and the individual's relation to it, and developmental theories.

A: Traditional Theories—Individual Characteristics

6. Sadism ("Sexual Thrill")

It might be said that those individuals who do not return trays are sadistic. That is, they seek and receive a kind of perverse sexual thrill from an act of aggression. Assuming that the act of aggression is against the administration, not returning trays would be somewhat like teasing a caged animal: the principal could snarl about the situation over the public address system, but this expression of anger or frustration on the part of the principal would only encourage tray-leaving. Perhaps the best he can do is to expel the student offenders.

7. Masochism ("Asking for Punishment")

A reverse interpretation could also be generated from a psychoanalytic image of man: perhaps the individuals who leave their trays unconsciously *want* to be punished. Hence they transgress: as Freud put it, the masochist, "In order to provoke punishment . . . must act against his own interests, ruin the prospects which the real world offers him, and possibly destroy his own existence in the world of reality."[13] As another psychoanalyst has put it, "Unconscious wishes to be raped, punished, beaten or devoured may all contribute to rebelliousness."[14]

This interpretation is somewhat similar to the psychoanalytic idea that crimes may be motivated by an overpowering existing sense of guilt, a desire to be punished.[15] The individual not only receives relief and gratification from the realistic criticisms he now can direct at himself, his deviant acts also involve the external world in a kind of ploy to assist him in self denigration. Perhaps ignoring the behavior would be effective—the masochist would seek his punishment elsewhere. (Although, perhaps a refusal to punish would make tray-leaving especially gratifying to the masochist—as in the old joke: "Hit me," said the masochist. "No," said the sadist.)

8. Narcissistic Gratification ("Attention-Seeking")

It is also possible, of course, that neither aggression nor sadism is involved at all. We have all heard parents say of children who misbehave or are fussy that they are "just looking for attention." Perhaps it is so in this case as well: desiring recognition from his environment, and unable to obtain it in other ways, a lonely or troubled individual might commit deviant acts so that he can at least obtain some sort of personal relationship with someone. Providing alternative sources of attention and recognition might work.

10. Inadequate Identification with Parents

In psychoanalytic theory conscience is formed by identification with the parents. It may be that those individuals who do not return their trays tend to lack a conscience—in other words, they would have sociopathic tendencies and simply be "out for themselves." Inadequate identification with parents, then, is a companion theory to the earlier "virtue doesn't pay" explanation of the social learning perspective. It differs only in suggesting that inadequate identification with parents (rather than a permissive upbringing) is involved.[16] Perhaps therapy would help, although it has not proven too helpful with people with sociopathic tendencies.[17]

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[13] Sigmund Freud (1924) "The Economic Problem of Masochism" *The Standard Edition of the Complete Psychological Works of Sigmund Freud*, Vol. XIX, London: Hogarth Press, 1957, 157-170.

[14] Ludwig Eidelberg (ed.) (1968) *Encyclopedia of Psychoanalysis*, New York: Free Press, 369.

[15] Sigmund Freud (1916) "Some Character-Types Met With in Psychoanalytic Work" *The Standard Edition*, Vol. XIV, op. cit., 332-333.

[16] See Wright op. cit., Glueck and Glueck op. cit.

[17] Robert Martinson (1974) "What Works?—Questions and Answers About Prison Reform," *The Public Interest*, Vol. 35 (Spring 22-54.

11. Identification with Irresponsible Parents

Tray-leaving would not be predicted only by inadequate identification. It may arise because the same sexed parent (with whom the child presumably identified strongly in childhood) did not take the responsibility for his own behavior, or was cruel, harsh, unprincipled, or self-serving.[18] Both this theory and the preceding one would suggest that, in the long term, the school system should seek to induce parents to change their child-rearing practices.

B. Psychoanalytic Group-Centered Theories

12. "Us Against Them" (In-group solidarity supported by displacement of aggression (scapegoating) against out-groups)

The traditional energy model of the human mind in psychoanalytic theory posits the existence, within each individual, of a fixed quantity of aggressive and libidinal energies. These energies are thought to be *conserved* in the sense that they are always present and cannot be added to or destroyed. An individual's personality structure is constituted from how he apportions and organizes these energies. For example, he may express some in direct action; he may use some energies to keep the lid on other energies or impulses (repression); he may express some of them in a modified form (a mechanism called sublimation), or he may express them against some person or object other than their original target (a mechanism called displacement).

Freud, in his analysis of the psychic economy of groups, proposed that unalloyed group morale, cohesion, and loyalty were supported by the tendency of group members to displace their fund of aggressive tendencies toward outside groups. The love of group members for each other, in other words, becomes more pure as their aggressive energies are redirected more exclusively against outsiders and as love is withdrawn from the outsiders and diverted to members of the in-group. Freud put the sobering matter this way:

> When once the Apostle Paul had posited universal love between men as the foundation of his Christian community, extreme intolerance on the part of Christendom toward those who remained outside it became the inevitable consequence.[19,20]

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[18] See Wright, op. cit., Glueck and Glueck, op. cit.

[19] Sigmund Freud (1930) *Civilization and Its Discontents*, in *The Standard Edition*, op. cit. Vol. XXI 114-115.

[20] See also the excellent review of other theoretical approaches to the in-group out-group problem in Robert A. LeVine and Donald T. Campbell (1972) *Ethnocentrism: Theories of Conflict, Ethnic Attitudes, and Group Behavior*, New York: Wiley.

More recently, in the case of Nazi Germany, it has been proposed that the high morale and unity of the German state was sustained by "scapegoating" the Jews, the invention of a common enemy helping to unify the German people. A familiar theme in science fiction movies during the Cold War was based on the same notion: the threat from outer space dissolves normal political conflicts as all nations unify in joint effort against the common alien enemy. In a somewhat attenuated form this same dynamic often can be seen in high schools: nothing, it seems, is associated with high morale or school spirit as much as a football team or basketball team which regularly defeats opposing schools.

This body of speculation, the "in-group solidarity sustaining aggression against out-groups" hypothesis, suggests that the individuals who leave trays will be found to be close friends of other individuals who leave trays. Their common aggression against others would be in the service of sustaining their bonds with one another.

If this "we-against-them" dynamic is the explanation of tray-leaving the most obvious policy recommendation, similar to that discussed earlier under social learning theory—("Evil Companions")—would be to adopt a policy that would alter these associations (e.g. rotation of lunch shift assignments).

13. Inadequate Identification With the School or Principal

A second group-centered hypothesis utilizing psychoanalytic theory would focus upon the school itself and posit that students who do not return their trays have an inadequate identification with the school. In other words, they do not feel the welfare of the school as their own welfare, they are not personally concerned when the school has a problem.

I said earlier that my high school principal implicitly used a behavior reinforcement theory when he put teacher monitors in the cafeteria to catch students who did not return their trays. In fact he also adopted an "inadequate group identification" theory. He felt that deviating individuals had insufficient pride in their school and so, at the time he announced the creation of teacher monitors over the school public address system, he tried to increase identification with the school and to utilize this dynamic to change behavior. He spoke *glowingly* of the great history and high ideals of Walter Johnson High School. He spoke *darkly* of "those few individuals," that "minority of students," who did damage to these ideals. He spoke *fervently* of his hope that all of us could once again feel pride in our school and strengthen its great traditions and ideals.

I must confess that, at the time, I felt somewhat embarrassed for the principal when he made this speech. My friends and I were too cynical—and, in our own minds, too intelligent—to be taken in by this kind of emotionalism. We were highly sensitive to being manipulated, and we suspected that he cared far more for getting those trays taken back than he genuinely cared about the "traditions" of a relatively new suburban high

school which had been in existence only seven years. But probably he truly believed what he said: it seems to be characteristic of conservatives to assume that social institutions have great traditions and high ideals.

14. Too Strong an Identification with the School (Identification with the Aggressor)

The previous theory argued that tray-leaving could arise from *weak* identification with the school. However the same behavior could also result from the opposite process, a *strong* identification with the school if individuals felt the school to be hostile or indifferent to them.

An illustration will make this dynamic clear. Bruno Bettleheim[21] reported on the behavior of other inmates he observed in Nazi concentration camps. He found that, far from opposing the brutality of the guards, there were some prisoners who actually began to imitate (identify with) the guards. Bettleheim interpreted this behavior as "identification with an aggressor," a psychological defense: rather than feel defenseless victims of their oppressors, the identification made inmates feel at one with them, a participant in their brutal power.[22]

If the "identification with an aggressor" hypothesis is correct we should think of those students who do not take back their trays as manifesting the same indifference and callousness toward the welfare of others as they feel the school system expresses toward them. The school system should become more benevolent.

C. Psychoanalytic Developmental Theories

By now we have crossed through two of the three groups of psychoanalytic hypotheses. Developmental theories, particularly focusing on adolescence, are relatively new (i.e. post Freudian) with the exception of the first to be considered (rebellion against authority).

15. Rebellion Against Parental Authority

In this perspective the school administration is seen as a parent surrogate (via "transference") and resentments against parental authority are expressed within the school. The "real" sources of tray-leaving would have to be sought in the home and the effective elimination of conflict in the home. Schools sometimes adopt this theory in recommending family counseling in the case of "behavior problems."

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[21] B. Bettleheim (1943) "Individual and Mass Behavior in Extreme Situations," *Journal of Abnormal and Social Psychology*, Vol. 38, 417-452.

[22] See also Anna Freud (1946) *The Ego and the Mechanisms of Defense*, New York: International Universities Press.

Psychoanalytic theory might also suggest, however, that rebelliousness is not an attempt to overcome *current* difficulties with authority in the home but, rather, an attempt to win old un-won battles from earlier in life which continue in the unconscious of the individual. Thus individual therapy might be required.

16. Deviation in the Service of Individuation

Deviant acts (like tray-leaving) may actually be committed by the individual in the service of obtaining a sense of himself as an individual who can act separately from the wishes of authority. In this sense tray-leaving, like other delinquent acts of adolescence, might be in the long term psychological interest of some individuals. Unlike a social learning approach (which would see anti-social behavior as something which the individual will continue if he "is allowed to get away with it") this ego development perspective would suggest that minor deviant acts are really a passing stage of development and may be quite beneficial in relation to the actual gains in a sense of personal identity and integrity which can accrue. It is sometimes argued that one of the benefits of juvenile gangs or friendship groups is the service they perform in this way by encouraging the individual to commit minor deviant acts, and by freeing him to commit these acts (reducing his guilt by sharing it).[23] Other unfortunate side effects (e.g. inhibitions in performing school work) have also been attributed to passive rebellion stemming from the same desire on the part of the individual to obtain or retain some sense of himself as a separate being.[24] We should note that, clamping down hard, the school might achieve short term gains but at longer term costs to the individuals' development.[25]

17. Separation Anxiety, Regression, and Structure Seeking (Anomie)

Rather than manifesting a positive developmental trend, however, adolescents who leave trays might do so from developmental difficulties and a cry for help. Progressing through adolescence involves a reduction in the external structures of life. An adolescent may face considerable

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[23] Erik Erikson (1966) "Eight Ages of Man" reprinted in Leon Gorlow and Walter Katkovsky (eds.) *Readings in the Psychology of Adjustment* (1968) New York: McGrew Hill, 297-317.

[24] Howard Halpern (1964) "Psychodynamic and Cultural Determinants of Work Inhibition in Children and Adolescents" *Psychoanalytic Review*, Vol. 51, 173-189; also Halpern (1969) "Psychodynamic Correlates of Underachievement" in Gloria and Monroe Gottsegen (eds.) *Professional School Psychology*, New York: Grune and Stratton, Vol. 3, 318-337.

[25] Note the considerable evidence suggesting the importance of providing an adult-influence, peer-influence *balance* in the interests of long term development of altruism and moral autonomy in Derek Wright, op. cit.

anxiety about the prospect of moving out on his own, choosing a college, getting a job, many may face a decision about marriage. If the individual is rushed into more freedom than he can handle, he may become increasingly anxious; he may have difficulty in concentrating or "getting it together," he may feel adrift or that he is sinking, unable to cope. For at least some people behavior can become bizarre, disorganized, or antagonistic without faith that someone else's firm hand is at the tiller. In this perspective the leaving of trays would be both a symptom of this kind of regression and a desperate, inchoate call for help—a desire to have benevolent authority step in, set down definite rules and structure, and thereby relieve the individual from his sense of being deserted.[26] If this theory is correct, then the principal should make rules and insist that this structure be adhered to: he will get his trays returned and also help his students.

18. Depression

The Group for the Advancement of Psychiatry has presented a psychoanalytic interpretation of depressive tendencies during adolescence in the following developmental perspective:

> The withdrawal from the parents normally causes a kind of mourning reaction or episodes of depression in the adolescent. Psychologically this is similar to mourning the actual loss of a loved person. Since the parents in fact are present, however, the cause of the depression is obscure to both the adolescent and his parents and is likely to be labeled simply as "moodiness."[27]

The GAP views these depression episodes as a consequence of growing independence, an increasing psychological separation from the parents. This depression could account, in turn, for why some people do not return their trays. It is not (as suggested earlier) that they are preoccupied, their energy directed elsewhere. On the contrary, they have no energy or desire to do anything.

Retrospect on Psychoanalytic Theories

I have not elaborated extensively on the separate policy implications of psychoanalytic theories. In large part this is because they bring very few good ones to mind except for sending tray-leavers to psychotherapy where they could learn more about their unconscious dynamics. Psychoanalysts themselves are notably reticent when it comes to suggesting policy alternatives other than psychotherapy.[28] I suspect, however, that much more could be done, reliably, in these directions. At a minimum, the trend toward including psychology as a part of the school curriculum seems hopeful.

[26] Robert K. Merton (1957) "Social Structure and Anomie" reprinted in his *Social Theory and Social Structure*, rev. ed; New York: Free Press, 131-160.
Sebastian DeGrazia (1948) *The Political Community: A Study in Anomie*, Chicago: University of Chicago Press.
Marshall B. Clinard, ed. (1964) *Anomie and Deviant Behavior*, New York: Free Press.

[27] Group for the Advancement of Psychiatry, *Normal Adolescence: Its Dynamics and Impact* (1968) New York: Scribners, p. 67.

[28] A useful discussion is Gaston E. Blom (1972) "A Psychoanalytic Viewpoint of Behavior Modification in Clinical and Educational Settings" *Journal of the American Academy of Child Psychiatry*, 11:4 (October) 676-693.

IV. Dramaturgical and Role Theory ("All the World's a Stage")

Dramaturgical and role theories, as their names imply, imagine that people are continually playing roles. These roles are *clusters* of behaviors and perspectives. In the role theory perspective, an individual does *not* perform a given action because he enjoys it (although he may), rather he acts the way he does because that is the role he is playing. And individuals do not necessarily adopt their roles because they find the roles, in sum, more gratifying than alternative roles. Rather they simply feel that it is *their* role or the *appropriate* role, a part of their identity.

19. Act/Scene Ratio

Most of the dramaturgical or role hypotheses to be discussed here invoke the name of different roles. One hypothesis, however, differs from these. This is the notion advanced by Kenneth Burke[29] that:

> From the motivational point of view, there is implicit in the quality of a scene the quality of the action that is to take place within it. This would be another way of saying that the act will be consistent with the scene.

If we pause to reflect on the scene provided by my high school cafeteria it is apparent that there was considerable impersonality, a rather objectionable institutional air about the long rows of formica topped tables and nondescript (sometimes broken) wooden chairs: it was noisy, the walls were made of cinder block with a dreary light green glaze. Burke would suggest that we would be more likely to find rather callous impersonal behaviors (like leaving trays) in this impersonal, institutional setting.

We would need, to be rigorous, to identify some other characteristic to go with Burke's hypothesis since people differ in their actions in the same setting. One avenue might be to explore personality factors that cause

[29] Kenneth Burke (1945) *A Grammar of Motives*, New York, 6-7.

individuals to differ in their susceptibility to being influenced by the scenes in which they are a part.

If Burke is correct, then the solution to our problem would lie in introducing a degree of *elegance* into high school dining. Tablecloths, noise dampening materials, flowers, carpets, etc. would provide different cues and produce a setting where people would be more inclined, automatically, to return their trays.

20. "Loser"

It is said that people can come to play the role of "Loser" in their lives. In formal language, we would say that they have developed a "negative identity" and that they go through life always calibrating their behavior so that they will be looked down upon by other people.

Jeanne Maracek and David Mettee[30] recently published experimental work which substantiates the concept of a "loser" syndrome. Subjects performed an experimental task and were told that they had done exceptionally well. The subjects then had a chance to perform the task again and, consistent with a loser syndrome prediction, those subjects who already had a strong sense of low self-esteem did make substantially more errors on the second performance of the task. In other words, knowing what the standards for success were, these losers unconsciously modified their behavior so they would tend to fail.

The possibility of a loser syndrome has also concerned Kai and Erik Erikson,[31] and they have applied the idea in recommending changes in policies for dealing with juvenile delinquents. Their concern is that if an adolescent is caught and punished he may develop a negative identity—he may begin to think of himself, in other words, as a loser or as a criminal or an outcast. Having labelled the adolescent a "loser," then, society is engaging in a self-fulfilling prophecy because the adolescent will tend to act out this identity in the future. (Women's Liberation writers have used a similar idea in criticizing the constrained roles and self-fulfilling prophecies inflicted on women in our society.)

There is, in fact, some intriguing additional evidence which supports the idea that you can establish a negative identity in a transgressor by catching him and punishing him and that, as a result, he will transgress more in the future than if you had not caught him and punished him. For example, a study in a British boarding school for boys compared two groups of boys with identical past histories for smoking. The only difference between the groups was that the boys in one group had, at one time or another, been

[30] J. Maracek and D. Mettee (1973) "Avoidance of Continued Success as a Function of Self-Esteem, Level of Esteem Certainty, and Responsibility for Success," *Journal of Personality and Social Psychology*, 22:1, 98-107.

[31] Erik Erikson and Kai T. Erikson (1957) "The Confirmation of the Delinquent" *Chicago Review*, 15-23.

caught smoking (which was against the rules of the boarding school) and had been punished for it. In this group which had been caught smoking and punished for it, a great number of boys were *still* smoking several years later.[32]

Research bearing on the "loser" syndrome suggests two ideas. First, the school itself may bear responsibility for establishing these negative identities. If so, we would expect to find that those individuals who do not return their trays have been given a great many negative cues over the years by the school system: low grades, for example, could establish negative identities, roles which individuals then act out in the cafeteria.[33]

The second idea a loser syndrome suggests is that the use of coercion and punishment will be a serious error. For, if tray-leavers are caught and punished, this can strengthen a sense of negative identity. Perhaps the school administration would succeed, to some extent, in getting the cafeteria problem under control—but it might do so at the cost of increasing other behavioral, academic, and developmental difficulties for those whom it punishes.

21. Peter Pan Syndrome

Peter Pan did not want to grow up. He wanted to stay young forever. If we infer from the story, we might imagine that he conceived growing up as equivalent to becoming like the awful Captain Hook, and his wish to stay young was a desire to avoid playing this kind of role.

I have chosen the illustration of a "Peter Pan Syndrome" deliberately because one of the major observers of modern youth, Kenneth Keniston, has proposed something quite similar. Young people today, he writes, believe that "beyond youth lie only stasis, decline, foreclosure, and death."[34] Young people balk at joining the "establishment" because to them this means playing a role which has extremely negativistic connotations. Responsibilities, in short, are seen as burdens; being mature is no fun.

The Peter Pan Syndrome suggests that those individuals who do not take back their trays confront a choice, in their own minds, between two

[32] J. W. Palmer (1965) "Smoking, Caning, and Delinquency in a Secondary Modern School," *British Journal of Preventive School Medicine*, Vol. 19, 18-23.

[33] In Sennett and Cobb's analysis "losers" tend to band together in friendship groups where they establish their own standards for recognition separate from—and often antagonistic to—the school's values (e.g. toughness, recalcitrance, etc.). The "losers" thus establish an insulated counterculture which salvages some degree of self-regard. A similar esteem enhancing function may occasionally be served on college campuses by some drinking fraternities: not everyone can make A's in class; but anybody can get plastered and brag about all of the silly things he did. See Richard Sennett and Jonathan Cobb (1972) *The Hidden Injuries of Class*, New York: Knopf.

[34] Kenneth Keniston (1971) *Youth and Dissent*, New York: Harcourt Brace Jovanovich, 17.

roles. The first role, the one they elect to play for themselves, is a role of freedom, moderate irresponsibility, emotional spontaneity, variety, and fun. The role they reject is a role which they see as oppressive, deadening, mechanical and rather boring and tiresome. In the choice between life and death those who leave their trays have elected life.[35]

Perhaps, if the adults in the school were to become more alive and fun-loving, they would provide models different from Captain Hook. Few of them, at least in my high school, seemed very joyful about their work.[36]

22. Game Playing

One additional hypothesis illustrating a role theory perspective is the notion of a game in which students and administration are each playing a part according to certain time-honored but unwritten rules. In this perspective the game "Who Will Return the Trays?" is a fun-filled pastime for the students involved. They leave trays, the principal growls about it over the public address system, teacher monitors are put into the cafeteria. But students continue to play the game with their own countermoves: watching for when the teacher monitor is looking in the other direction before exiting for their next class (leaving their trays behind them). Of course the student knows that, if he is caught leaving his tray, nothing particularly serious will happen—he might get an angry word, or, at worst, he might have to go to a detention study hall: it would be like a game of ice hockey in which an offender can be caught in a transgression and will go to the penalty box briefly but knows he will rejoin his teammates in the game after awhile. The "Return the Trays" game the students play with the administration could be seen, in this light, as similar to other games students play in high school classrooms with teachers—for example, the "Who's Done Their Assignment for Today?" game (in general, in my high school, few students had done their assignments—and the ball then was back in the teacher's court and he or she had to figure out a countermove).

Note that it is not necessary for both students and administration to play the game. What is necessary is only that students see it as a game. In fact, if they do see "Who Will Return the Trays?" in this way, I am not

[35] Some psychologists would see the Peter Pan Syndrome as calling for psychotherapy. Through it, Pearce and Newton argue, "The grim concept of social responsibility is transformed into pleasure in the privilege of social participation on as wide a base as the person's capacities will permit." See Jan Pearce and Saul Newton (1963) *The Conditions of Human Growth*, New York: Citadel Press, 444.

[36] What may be involved is a special case of the distinction sociologists draw between "up front" and "back stage" behavior. Restaurant managers, for example, can be quite irreverent and fun-loving when they are behind the scenes; but they become somber and a bit stiff when they appear before their official audience of customers. See, for example, Erving Goffman (1959) *The Presentation of Self in Everyday Life*, New York: Doubleday, 119.

sure what the administration could do about it. If the principal were to announce over the public address system, "Look, I'm not going to play games—I want those trays taken back," he might have little effect. Students (at least at my high school) would likely have seen such a statement by the principal as a particularly clever countermove, only a shrewdly calculated attempt to win the game by pretending there was no game.

V. Humanistic Psychology

Humanistic psychology views men as having an innate tendency to "grow," a term which is usually taken to mean becoming more humane, altruistic, productive, loving, and so forth. If we view not returning cafeteria trays as indicative of some blockage in the growth process, Abraham Maslow's work suggests two hypotheses:

23. Lower Need (e.g. Sexual) Deprivation

Maslow views men as being motivated by a hierarchy of needs—the "higher" needs motivate only when lower needs are satisfied.[37] If returning trays is seen as indicative of a "higher" (more altruistic) motivation, then not returning trays might arise from the deprivation of any of the "lower" needs—of which sexual satisfaction is, in Maslow's view, one. Thus we would expect that the students who do not return trays are those who are more sexually frustrated and deprived, and a high school administration which wanted to deal with the cafeteria tray problem would have to concern itself with facilitating adequate sexual satisfaction for its students. I suspect, however, that it will require higher consciousness on the part of school administrators before they are willing to consider this theory seriously. They were most reluctant, at least in my day, even to acknowledge the existence of what one of them called (privately) "the ultimate relationship."[38]

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[37] Abraham Maslow (1970) *Motivation and Personality*, New York: Harper and Row, revised edition.

[38] An excellent study of some of the political problems connected just with providing accurate sex education is provided by Mary Breasted (1970) *Oh! Sex Education*, New York: Praeger. See also Lester A. Kirkendall (1969) "The School Psychologist and Sex Education," in Gloria and Monroe Gottsegen (eds.) *Professional School Psychology*, Vol. 3, New York: Grune and Stratton, 148-171.

24. The Jonah Complex

Maslow also writes that many people fear their highest potentialities.[39] They do not feel *strong* enough to feel too good about themselves, too noble or virtuous or competent. Counter to what Keniston would say (The Peter Pan Syndrome) or what a social learning theorist would say, taking back trays *is* seen as psychologically rewarding by these people but they avoid the behavior because they could not stand that much gratification.

[39] Abraham Maslow (1968) "The Jonah Complex" in Warren Bennis et al. (eds.) *Interpersonal Dynamics*, New York: Dorsey, rev. ed. See also Sigmund Freud's related discussion of people who are destroyed by success, (1916) "Some Character Types Met With in Psychoanalytic Work" in *The Standard Edition*, Vol. XIV, op. cit., 316-331.

VI. Specialized Theories

There are six rather specialized theories that can be applied to the tray problem: emotional contagion, reduced altruism from sensory overload, equity theory, Kohlberg's theory of moral development, depersonalization theory and frustration-aggression theory.

25. Monkey See/Monkey Do (Emotional Contagion)

Classic analyses of human behavior in large groups point to a range of phenomena which occur in these settings.[40] One is the phenomenon of emotional contagion—behavior and feelings spread more rapidly. If this mechanism operates in the cafeteria (perhaps with some being more susceptible than others) then we would simply say that, somehow, the act of not returning trays got started—and it spread. If emotional contagion of this sort occurs in the high school cafeteria one solution might be to partition the single large room into a series of smaller rooms, thus reducing the extent to which individuals are part of a large mass.

26. Sensory Overload and Reduced Altruism

One of the traditional hypotheses about life in large cities is that there is so much sensory stimulation (e.g. noise, large numbers of people, activity), that people have to reduce their emotional involvement with (and concern for) most of the people they meet in order to retain some kind of equilibrium.[41] Thus we would expect (assuming some individuals reduce their emotional involvement with their environment more strongly than others) that not returning cafeteria trays would be a result of the

[40] See for example Gustav Le Bon (1903) *The Crowd*, London: Unwin.

[41] Georg Simmel (1950) "The Metropolis and Mental Life" in Kurt W. Wolff (ed.) *The Sociology of Georg Simmel*, New York: Free Press, 409-424.
Stanley Milgram (1970) "The Experience of Living in Cities," *Science*, Vol. 167, 1461-1468.

crowded conditions in the cafeteria (and perhaps in the school in general). The effective resolution of the tray problem, by this theory, would be to reduce crowding, install sound deadening materials, etc.

27. Kohlberg Moral Development Theory

Kohlberg has advanced considerable evidence for a new theory which sees moral development occurring in a sequence of six stages.[42] He has studied moral *reasoning* (how a person explains or justifies an act as moral or immoral), but the stage theory seems also to predict to moral *behaviors* as well.[43] One of the lower stages of moral development is hedonistic morality (i.e. moral appropriateness is derived from the "what's in it for me" attitude identified earlier as an assumption in social learning theory).

The highest stage is the stage of individual ethical principles (the individual makes up his own mind in a principled way about what is right or just), and greater altruism and sense of individual responsibility seem to be associated with this stage as well. Kohlberg's theory would tell us that those who leave their trays may be at a lower level of moral development. The solution to the problem then would be careful attention by the school to curriculum innovations that would move students to higher stages of moral development. (This task apparently cannot be done by simple exhortation.)[44]

28. Equity Theory (Golden Rule Psychology)

Equity theory is probably best expressed, in its basic form, by the *lex talonis* of antiquity, "An eye for an eye, a tooth for a tooth." In other words, it is the proposition that, to the extent they can, people are motivated to repay others, to behave toward others the way others behave toward them. If you treat others with kindness and respect, the theory proposes, they will treat you with kindness and respect. Give them a hard time and they will tend to give you a hard time when they have the opportunity.[45]

In the case of the unreturned cafeteria trays equity theory would tell us that students were expressing a basic and situationally-induced resentment

[42] L. Kohlberg (1969) "State and Sequence: The Cognitive-Developmental Approach to Socialization" in D. A. Goslin (ed.) *Handbook of Socialization Theory and Research*, Chicago: Rand McNally.

[43] N. Haan, M. B. Smith, and J. Block (1968) "The Moral Reasoning of Young Adults," *Journal of Personality and Social Psychology*, Vol. 10, 183-201; James Fishkin et al. (1973) "Moral Reasoning and Political Ideology," *Journal of Personality and Social Psychology*, 27.1, 109-119.

[44] See Derek Wright, op. cit., chapter 10; also, E. Turiel (1966) "An Experimental Test of the Sequentiality of Development Stages in the Child's Moral Judgements," *Journal of Personality and Social Psychology*, Vol. 3, 611-618.

[45] Elaine Walster et al. (1973) "New Directions in Equity Research," *Journal of Personality and Social Psychology*, 25:2, 151-176.

against the school: the regimentation, low marks, boredom, large classes, and a somewhat authoritarian structure are inducing them to repay the school for the hassles and indignities to which they have been subjected.

It is interesting, in this connection, to observe that equity theory would predict that the only way to resolve the problem would be to make high school a place where students are treated with respect and dignity, a great many rewards are forthcoming, and so forth. Only if the administration lives up to the Golden Rule will students do likewise. Note that the use of coercion or punishment is very unwise if equity theory is correct since these will only motivate further student underground resistance in either the classroom or the cafeteria.

29. Depersonalization

An increasing number of studies point to the possibility that depersonalization and anonymity tend to dissolve the obligations and humanizing restraints in individual conduct.[46] If so, we would expect to find those leaving their trays to be students who receive less recognition from the school, to be the "forgotten," ignored students, the ones for whom neither teachers nor administrators have time.[47]

Interestingly, there is now some general evidence for a depersonalization theory. Not only are students "depersonalized," it appears that school administrators and teachers are not seen as fully human, at least by high school students—a condition which may further promote callousness and indifference toward them.[48] If depersonalization theory is correct then a principal should concern himself with reducing the impersonal, bureaucratic atmosphere of the school. Students must feel known, recognized, and cared about; and they should feel those who run the school are "personalized" human beings engaged in honest human relationships rather than role performances.

30. Frustration-Aggression

If we think of leaving trays as an aggressive act, then perhaps frustration-aggression theory can help us to understand it.[49] What might

[46] L. Festinger, A. Pepitone, and T. Newcomb (1952) "Some Consequences of Deindividuation in a Group," *Journal of Abnormal and Social Psychology*, Vol. 47, 382-389; P. G. Zimbardo (1969) "The Human Choice: Individuation, Reason and Order Versus Deindividuation, Impulse and Chaos," in D. Levine (ed.) *The Nebraska Symposium on Motivation, 1969*, Lincoln: University of Nebraska Press.

[47] Paradoxically, the large modern high school was developed, in part, from a desire for efficiency—yet this very "efficiency" of bigness may carry with it depersonalization and larger costs in vandalism and anti-social behavior.

[48] Derek Wright (1962) "A Comparative Study of the Adolescent's Concepts of His Parents and Teachers," *Educational Review*, Vol. 14, 226-232.

[49] John Dollard et al. (1939) *Frustration and Aggression*, New Haven: Yale University Press.

produce the frustrated students who, the theory holds, would be likely to express their frustration as aggression against the school? It *might* be that the most objectively deprived students would be the most frustrated. But the available evidence suggests that frustration may depend instead on *relative* deprivation, that is the gap between what a man wants or feels entitled to receive and what he actually does receive.[50]

As with equity theory, one possible solution is to increase the rewards to students, thus reducing frustrations. However if *relative* deprivation is involved, then several other alternatives become plausible depending on how students form their comparison levels:[51] one alternative might be to equalize existing rewards so that students would not face invidious comparisons with one another. Or the school might de-emphasize the achievement ethic: rather than dangle the carrot of an idealized academic success in front of many students who can never achieve it, the school could adopt a more humanistic set of ideals that everyone could meet; paradoxically, it may be that high standards, by inducing a sense of inadequacy and frustration, turn out to be counterproductive. Or the problem might be a lot simpler than this, a matter of providing better food in the cafeteria.[52]

[50] L. Berkowitz (1972) "Frustrations, Comparisons and Other Sources of Emotional Arousal as Contributors to Social Unrest," *Journal of Social Issues*, 28:1, 77-91.

[51] Leon Festinger (1954) "A Theory of Social Comparison Processes," *Human Relations*, Vol. 7, 117-140; David Sears and John McConahay (1973) *The Politics of Violence: The New Urban Blacks and the Watts Riot*, Boston: Houghton Mifflin.

[52] It is possible that special privileges for teachers and administrators are sources of student frustration—in some high schools teachers are allowed to cut in the front of the long cafeteria lines, they have lounges where they can smoke, etc.

VII. Field Theory: Different Strokes for Different Folks?

I have reserved discussion of field theory until the end because it does not offer specific hypotheses. Rather it offers a general perspective on the hypotheses that have preceded.

Field theory asks that we imagine each individual as living in a psychological "life space," a psychological space which includes a variety of personal and situational *forces* that, in combination, determine behavior.[53] Field theory alerts us that our preceding theories are *not* mutually exclusive. In the same individual there may be a "what's in it for me" attitude, a tendency to be deviant in the service of developing a greater sense of his own identity, a mild degree of depression, certain sadistic tendencies, a loser syndrome, some susceptibility to emotional contagion (and so forth). *All* of these factors (and perhaps others affecting him in opposite directions) may be at work and, by their sum, produce the final behavior we observe.

By proposing the image of *separate* individual life spaces, field theory also alerts us that the relevant constellation of forces—the presence or absence of particular forces and their strength if present—may well differ from individual to individual. To account fully for tray-leaving, then, we *may* need all of the theories reviewed so far (not to mention others that might have to be discovered). We might need a somewhat different explanation for each individual.[54] And we might need to find a variety of "solutions," each of which will affect somewhat differently the behavior of different individuals.

It is important to emphasize, however, that field theory only *suggests* this maximum complexity might be present. It does *not* rule out, on

[53] Deutsch and Krauss, op. cit.

[54] G. A. Kelly (1955) *The Psychology of Personal Constructs*, 2 Vols. New York: Norton.

theoretical grounds, the possibility that a few factors might actually account for most of the differences between the people who return trays and those who do not.

VIII. Thirty Theories in Search of Reality

Perhaps the reader is a bit dazed by now, finding that he has been forced to withdraw some of his attention as theories piled up and stimulus overload became a reality. It will be well, then, to call a halt at this point. I have diagrammed the thirty theories in Figure 1.[55]

A quick glance at the diagram shows that many linkages are still unstated, especially how background factors in individual development affect variations in fun seeking, certain unconscious dynamics, social conformity, and physiological responses. There are, of course, other theories about all of these things, but it would add little to go into them here: the purpose has been to inventory and introduce basic traditions of explanatory theory, not to write an exhaustive anatomy.

I do want to indicate, however, that there are several avenues I have not explored. There is the Marxist theory of a possible "haughty bourgeoisie indifference" of some students toward the working class employees of the cafeteria and the Maoist policy solution of decreasing depersonalization, altering rewards and punishments, and increasing identification by requiring the students to serve as workers and all members of the school to engage in public mutual and self-criticism sessions. More importantly, I have made the implicit assumption that returning trays is desirable behavior: reversing this assumption could turn up disquieting syndromes

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[55] A thoughtful, exceptionally useful map for the analysis of personality effects on politics is M. Brewster Smith (1968) "A Map for the Analysis of Personality and Politics," *Journal of Social Issues*, Vol. 24, 15-28.

My map, for reasons of simplicity, ignores the possibility that the factors which sustain behavior may be different from those that first start it (e.g. a "try it, you'll like it" mechanism). One one way in which behavior, once instituted, can change its psychological meaning see the discussion of cognitive consistency and self-attribution in Daryl Bem (1970) *Beliefs, Attitudes and Human Affairs*, Belmont, Calif.: Brooks/Cole. I am endebted to Gary Wolfsfeld for a discussion of these additional complexities that should be included in an exhaustive analysis of possibilities.

that might characterize some students who *return* their trays—e.g. automatic "authoritarian" obedience of anyone in authority.[56]

But I think we have surveyed the major theories. Taken together in the map they show the types of factors which potentially interact to affect a single behavior in one person: his *individual background*, the broader *context* of the society and social institutions of which he is a part, his *motives and inner states* in all their complexity, the many facets and dimensions of the *immediate situation*.

Anyone reading social science literature or the popular press will encounter different authors beating the drums for different theories: cost-benefit theories of voting, inadequate child-rearing as a theory of crime, theories of unconscious determinants of war and so forth. A map such as that in Figure 1 may be useful in keeping all of these different ideas in an organized perspective. And the complexity of the map demonstrates why the professional social scientist, although he values individual insights, nevertheless wants hard evidence before he will believe any one plausible theory is a major explanation.

Possibly it requires a sense of humor to consider a minor problem like unreturned cafeteria trays from thirty different points of view. But the important point is that most major problems of human behavior have an analogous structure: some people are criminals but others are not, some nations go to war but others do not, some people find society alienating but others do not, some students think and work up to their potential but others do not, some people are racially prejudiced but other people are not. The thirty different theoretical perspectives identified different policy alternatives and strategic intervention points which men of good will might use to solve such problems and make this a better world. These policy options are summarized in Table 1.

Some of these thirty theories might be called "conservative" theories: they attribute the cause of the problem to something about individuals and they recommend intervening to change individuals to solve the problem. Other theories could be called "liberal" theories: they attribute the cause of the problem more to the surrounding social structures and practices and they recommend intervening to change this environment to solve the problem. It is true, in America, that each individual has the right to advocate his ideology through an equal vote in the decision-making process. But embedded in liberal and conservative perspectives are theories of human behavior: from the viewpoint of a social scientist the best way to decide among theories is to assemble evidence, not dismiss them (or champion them) because they fit the relatively uninformed prejudices and partial insights that have been the traditional guidelines for resolving policy questions in our society.

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[56] T. W. Adorno et al. (1969) *The Authoritarian Personality*, New York: Norton.

Figure 1.

A MAP FOR THE ANALYSIS OF ONE INDIVIDUAL'S TRAY-LEAVING BEHAVIOR

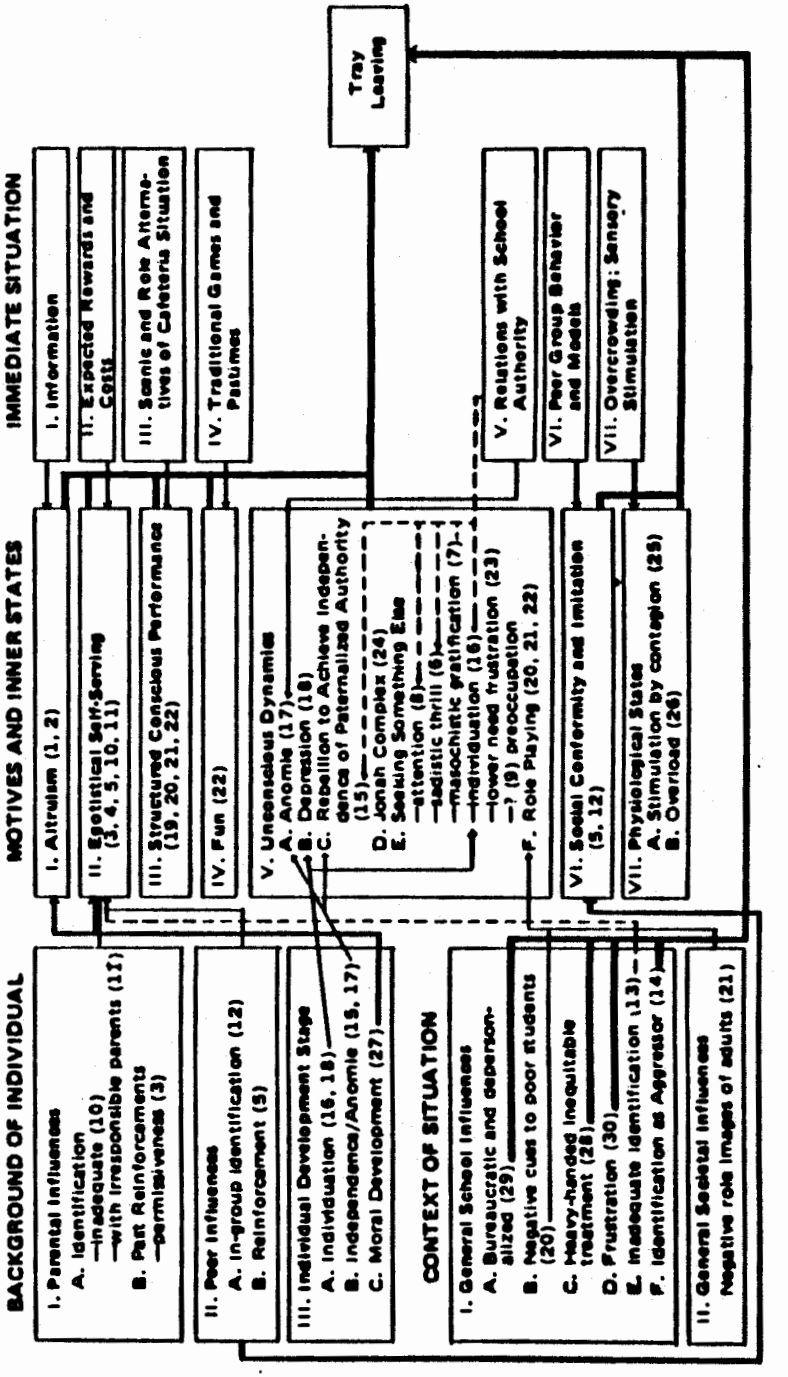

Table 1

Theories and Policy Options: A Summary

Theories	Policy for Behavior Change
I. Cybernetic	
1. Ignorance of Expectations	Information about expectations
2. Ignorance of Consequences	Information about consequences
II. Behavior Reinforcement	
3. Permissive Up-Bringing	Better reinforcement schedules by parents
4. What's In It for Me?	Deposit system; give rewards if possible; increase costs
5. Small Group Rewards	Breakup groups, use student government to exert peer group pressure
III. Psychoanalytic Model	
6. Sadism	Therapy; Expulsion
7. Masochism	Therapy; Ignore it (?)
8. Attention Seeking	Therapy; Alternative source of attention
9. Preoccupation	Reminders
10. Sociopathic Tendencies	Therapy (?); better child rearing
11. Identification with Irresponsible Parents	(?); better child rearing
12. In-group/Out-group	Break up groups
13. Inadequate Identification with School or Principal	Strengthen identification with school; better leadership
14. Identification with School as Aggressor	Increase benevolence of school system
15. Rebellion Against Parental Authority	Family or individual therapy
16. Deviation in the Service of Individuation	Therapy
17. Separation Anxiety, Regression, Structure Seeking (Anomie)	Strengthen and enforce rules; Therapy
18. Depression	Therapy
IV. Dramaturgical/Role Model	
19. Act/Scene Ratio	Add elegance to high school dining
20. "Loser"	Therapy
21. Peter Pan Syndrome	Better role models, (fun loving but responsibility, charisma)
22. Game Playing	(?)
V. Humanistic Model	
23. Lower Need (e.g. Sexual) Deprivation	Provide or facilitate meeting of unmet needs; sex; sex education
24. Jonah Complex	(?)
VII. Specialized Theories	
25. Emotional Contagion	Break large room into small sections
26. Sensory Overload and Reduced Altruism	Reduce pace of life, noise levels, crowding; break large room into small sections
27. Kohlberg Moral Development Theory	Design curriculum innovations to facilitate development of moral reasoning
28. Equity Theory (Golden Rule Psychology)	Provide more overall rewards from school system; better and more attractive food; *don't punish!*

Table 1. Theories and Policy Options: A Summary (continued)

Theories	Policy for Behavior Change
29. Depersonalization	Break up large schools; more personal interest of staff in all students; facilitate seeing cafeteria and other staff as individuals
30. Frustration/Aggression	More rewards from school system; equalize rewards; de-emphasize achievement ideals in favor of more humanistic ones; eliminate special privileges for staff.

Additional Readings

I. How Decisions Are Made in American Government

Charles E. Lindblom (1968) *The Policy Making Process*, Englewood Cliffs: Prentice Hall.

Aaron Wildavsky (1964) *The Politics of the Budgetary Process*, Boston: Little, Brown.

Graham Allison (1971) *Essence of Decision: Explaining the Cuban Missile Crisis*, Boston: Little, Brown.

John Steinbruner (1974) *The Cybernetic Theory of Decision*, Princeton: Princeton University Press.

II. How American Government Sometimes Uses Social Science Theories

Peter Marris and Martin Rein (1973) *Dilemmas of Social Reform*, Chicago: Aldine, second edition.

Daniel P. Moynihan (1973) *The Politics of a Guaranteed Income*, New York: Vintage.

III. Some Additional Case Study Material on Public Policy Formation

Theodore Marmor (1973) *The Politics of Medicare*, Chicago: Aldine Publishing Company.

Eric Redman (1973) *The Dance of Legislation*, New York: Simon & Schuster, Inc.

Jeffrey Pressman and Aaron Wildavsky (1973) *Implementation*, Berkeley: University of California Press.

Eliot, Chambers, Salisbury and Prewitt (1965) *American Government: Problems and Readings*, New York: Dodd, Mead & Co.

IV. Theories in Social Psychology and Political Science

Morton Deutsch and Robert M. Krauss (1965) *Theories in Social Psychology*, New York: Basic Books.

Oran R. Young (1968) *Systems of Political Science*, Englewood Cliffs: Prentice Hall.

Mancur Olson (1971) *The Logic of Collective Action*, Cambridge: Harvard University Press.

Thomas Schelling (1963) *The Strategy of Conflict*, Oxford: Oxford University Press, Chapter 2.

Murray Edelman (1964) *The Symbolic Uses of Politics*, Urbana, Ill: University of Illinois Press.

Analysis Topics–
The Case of the
Unreturned Cafeteria Trays

I. Applying the Arguments of Different Theories

1. Social Learning Theory

A Marxist might say that a market mechanism solution to any social problem is inherently immoral because it sanctions individual selfishness and greed as the determinants of behavior. Would you agree or disagree?

2. Inadequate Identification and Depersonalization

A Marxist might find it significant that most students in my high school were middle class or upper-middle class; 85% went on to college. The cafeteria workers and janitorial staff were blue collar "functionaries." Do the actions of the students who leave their trays display an indifference and callousness toward these people that is a part of any class system? How does the Communist Chinese government attempt to prevent the development of "bourgeoise arrogance" in its citizens?

3. Game Playing

In a sense the student government in my case study was "playing politics." Were we morally right to do what we did, morally wrong, or do you think that perhaps moral judgements should not apply to "games?" What do you think about politicians who "play politics?"

4. Maslow Need Hierarchy Theory

Maslow would propose that a healthy and satisfying love life is one prerequisite for good citizenship. Does this sound far-fetched to you or does it sound accurate?

5. Moral Development Theory

For his book *Political Ideology*, Robert E. Lane conducted extended depth interviews with working class men. He found that those men who worried about their ability to control their own impulses favored strong, moralistic, law-and-order government. They seemed to be saying that they needed and wanted the threat and realistic fear of reprisal from government authority as an aid to deterring their own anti-social impulses. Kohlberg would agree that there are people like this. Clearly then the ideal of applying the same laws equally to all men is bad policy since the same laws and law enforcement practices can restrict unduly the people at the highest levels of moral development and be too lenient for those at the lower ends. Do you agree or disagree with this argument? Do you think police and courts already work on a rough-and-ready theory of this kind by giving out different punishments and enforcing laws differently for different groups?

II. Analyzing the Viewpoint of the Paper

1. The paper implies that liberals and conservatives are just deficient social scientists, that they advocate policies based on attitudes which embody theories for which they have no really good evidence. Is this characterization fair?

2. The paper implicitly argues that public policy should be based on good social science theory. What is the likelihood that such an approach would lead to totalitarianism or elitism? Is the approach anti-political?

III. Exercises in Thinking from Different Viewpoints

1. Some people in America make a very good living while other people are poor. Is poverty the fault of individuals or the fault of their environment? Propose three theories that would tend to blame the poor for their poverty and three theories that would tend to blame society.

2. Some people vote and others do not. Propose six alternative theories to explain this difference. (Note: do not automatically equate voting as a "good thing" analogous to returning trays.) On the basis of your political science courses, what theories are best?

3. Suppose that the Governor of your state appoints you to a special citizens' advisory committee on drunken driving. The Governor wants something done about the high loss of life due to the drunken driver problem. Your committee has $50 million to spend and a promise that the Governor will sponsor any constitutional laws that you propose. Outline five alternative approaches to solving the drunken driver problem.

4. Some people in other countries are revolutionaries opposed to "American imperialism." Other people are not. Propose five theories to explain this difference. Which theories do you think are best? What evidence can you offer to support your choice?

5. During the Kennedy administration the Russian government placed nuclear missiles on the island of Cuba. Propose seven alternative theories about why they might have done this.

Composition by TypoGraphics, Columbia, Maryland

Lloyd S. Etheredge - A Brief Biography

Lloyd S. Etheredge received his BA (Honors, Economics) from Oberlin College (1968) and his MA (International Relations, 1972) and Ph. D. (Political Science, 1974) from Yale University. His graduate education included interdisciplinary training in the Psychological Study of Politics program at Yale, with support by an NIMH Traineeship.

As a scientist, Lloyd Etheredge's interest is to develop rapid learning systems to accelerate scientific innovation and improve public policy decisions; and to develop social science research concerning wisdom and good outcomes as properties of the world's complex (sometimes) adaptive systems.

Dr. Etheredge received a graduate teaching award from MIT, where he was a member of the faculty for eight years. He has been Director of Graduate Studies for International Relations at Yale, with administrative and academic responsibility for a multi-disciplinary program.

Dr. Etheredge was awarded a Fellowship to the Center for Advanced Study in the Behavioral Sciences at Stanford in 1982-83; he was elected to the World Academy of Art & Science in 2004. He has held visiting faculty positions at the UC Berkeley, Duke University, the University of Toronto, and other leading institutions. He is the author or editor of four books and many other publications, including The Case of the Unreturned Cafeteria Trays (1976), "Hardball Politics: A Model"(1979), "On Being More Rational Than the Rationality Assumption . . ." [re the nuclear arms race and deterrence] (1992), "Wisdom in Public Policy" in Robert Sternberg and Jennifer Jordan (Eds.), A Handbook of Wisdom: Psychological Perspectives (NY: Cambridge University Press, 2005) and "Neuropsychology and Rapid Learning Systems about Social Problems" (2010).

In addition to teaching and scientific research, Dr. Etheredge has provided consulting, advice, and (sometimes) activist organizing and advocacy on behalf of social science applications to achieve the policy sciences goal of "a world commonwealth of human dignity." He is a member of the American Political Science Association, the Policy Sciences Society, the American Association for the Advancement of Science, and a Life Member of the American Psychological Association. He serves as Project Director at the Policy Sciences Center, Inc., a public foundation created in New Haven, CT in 1948 by Harold Lasswell and his associates. Copies of his published and policy work are available online at www.policyscience.net and www.policyscience.ws.

March 2014

CURRICULUM VITAE (Brief)
Lloyd S. Etheredge

DATE OF BIRTH: May 31, 1946

CITIZENSHIP: United States of America

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EDUCATION

Yale University	Ph.D. (Political Science)	1974
Yale University	M. Phil. (Political Science)	1972
Yale University	M.A. (International Relations)	1970
Oberlin College	B.A. (Economics, Honors)	1968

PROFESSIONAL EXPERIENCE

Director, International Scientific Networks and Government Learning Projects, Policy Sciences Center Inc. (a public foundation), New Haven, CT; 1991 - ; Consultant, 1995 - .

Visiting Associate Professor/Scholar: Oberlin College, American University, Duke University, Swarthmore College, University of Toronto, (1988 - 1992)

Director of Graduate Studies for International Relations, Yale University; 1986 - 1988

Visiting Professor and Associate Professor, Research Fellow/Scholar: Survey Research Center, University of California, Berkeley, Mills College, Rockefeller Institute of Government (SUNY-Albany) (1983-1986)

Fellow, Center for Advanced Study in the Behavioral Sciences, Stanford, 1982-1983

Associate Professor (Visiting), School of Organization and Management, Yale University, Spring, 1982

Associate Professor, Department of Political Science, Massachusetts Institute of Technology, 1979 - 1983; Assistant Professor, 1975-1979

Assistant Professor, Departments of Psychology and Political Studies, University of Manitoba, 1974-1975; Lecturer, 1972-1974

FIELDS OF INTEREST

Behavioral science and government learning rates (domestic and international); new communications/ information technology and the design of rapid learning systems; emerging applications of neuroscience to national security and domestic policy; policy sciences.

PROFESSIONAL ORGANIZATIONS (partial list)

Fellow - World Academy of Art & Science (elected, 2004 -); American Political Science Association (1972 - ; Chair, Helen Dwight Reid Award Committee, 1989); American Psychological Association (elected, 1981 - Life Member, 2012 -); International Society for Political Psychology (Founding Member, 1979 - ; Governing Council, 1985 - 1987, Editorial Board, 1979 - 1997, Nominations Committee, 1993, Chair, Harold D. Lasswell Award Committee, 1996); International Studies Association (1981 - ; Information Technology Planning Committee, 1993 - 1995; ISA Channel Committee, 1997 - 2000); American Economic Association (2004 -); Joint Program for Conflict Resolution (with Islamic Mental Health Association; Advisory Board, 1991 - 2007); Fellow, AAAS (1992 -); Internet Society (1994 -); New York Academy of Sciences (1996 -); Policy Sciences Center, Inc. (Trustee, 1994 - 2000); Society for the Policy Sciences (Founding Member 1995 - ; Executive Board, 1995 - 1998).

FELLOWSHIPS AND AWARDS

Fellow - World Academy of Art & Science (elected, 2004)

U.S. Department of State. Secretary's Open Forum Distinguished Public Service Award, 1998.

Ittelson Consultant, Group for the Advancement of Psychiatry - Committee on International Relations, Fall, 1988

Center for Advanced Study in the Behavioral Sciences, Fellowship, 1982-1983

Teaching Excellence Award, MIT Graduate Student Association, 1979

National Institute of Mental Health Traineeship Award, Yale Psychological Study of Politics Program, 1970-1971, 1971-1972

PUBLICATIONS [1]

1. Books and Book Chapters

"Wisdom in Public Policy" in Robert Sternberg and Jennifer Jordan (Eds.), A Handbook of

[1] A more complete list and reference copies of working papers and reports of my foundation projects are available online at www.policyscience.net and www.policyscience.ws.

Wisdom: Psychological Perspectives (NY: Cambridge, University Press, 2005), pp. 297 - 328.

"A Strategy for Human Rights: Five Internet Projects That Can Change the World" in George J. Andreopoulos (Ed.) Concepts and Strategies for International Human Rights (NY: Peter Lang, 2002), pp. 185 - 211.

_____ (Ed.) Humane Politics and Methods of Inquiry: Selected Writings of Ithiel de Sola Pool (New Brunswick, NJ: Transaction Books, 2000). Editor's introductions and "What's Next: The Intellectual Legacy of Ithiel de Sola Pool," pp. 301-316.

_____ (Ed.), Politics in Wired Nations: Selected Papers of Ithiel de Sola Pool. (New Brunswick, NJ: Transaction Books, 1998).

"Human Rights Education and the New Telecommunication Technology" in George Andreopoulos and Richard Claude (Eds.), Human Rights Education for the Twenty-First Century (Philadelphia: University of Pennsylvania Press, 1997), pp. 547 - 564.

"On Being More Rational Than the Rationality Assumption: Nuclear Deterrence, Public Drama Requirements, and the Agenda for Learning," in Eric Singer and Valerie M. Hudson (Eds.), Political Psychology and Foreign Policy (Boulder, CO: Westview Press, 1992), pp. 59-75.

Can Governments Learn?: American Foreign Policy and Central American Revolutions (NY: Pergamon Press, 1985).

"Government Learning: An Overview," in Samuel Long (Ed.), Handbook of Political Behavior, Vol. 2, (NY: Plenum Press, 1981), pp. 73-161.

A World of Men: The Private Sources of American Foreign Policy (Cambridge, MA: MIT Press, 1978).

2. Monographs and Papers in Refereed Journals (partial list)

"The Scientific Scandal of the 1980s," Political Psychology 15:1 (1994), pp. 534-539.

"Wisdom and Good Judgment in Politics," Political Psychology, 13:3 (1992). pp. 497 - 516.

"President Reagan's Counseling," Political Psychology, 5:4 (1984), pp. 737 - 740.

"The Hypnosis Model of Power," in Psychoanalysis and Contemporary Science, 3:3 (1980), pp. 415-451.

"Hardball Politics: A Model," Political Psychology, 1:1 (Spring, 1979), pp. 3-26.

"Personality Effects on American Foreign Policy, 1898-1968: A Test of Interpersonal Generalization Theory," American Political Science Review, 72:2 (June, 1978), pp. 434-451.

The Case of the Unreturned Cafeteria Trays (Washington: American Political Science Association, 1976).

PROPOSAL AND MANUSCRIPT REVIEWS (Partial list)

American Journal of Political Science
American Political Science Review
Canada Council
Canadian Journal of Political Science
Comparative Politics
Journal of Conflict Resolution
Journal of Interdisciplinary History
MacArthur Foundation (consultant)
MIT Press
National Science Foundation
Policy Sciences
Political Psychology
University of California Press
University of Chicago Press

June 2012