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Drugs, Market Size and Population

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FIGURES AND TABLES

Drugs, market size and population

Rodrigo Cerda *

April 30^{th}, 2002

Abstract

This paper addresses the upward trend in new drugs introduced by pharmaceutical firms, during the second half of the 20^{th} century. We indicate that the continuous increases in population, and thus in the market size of this sector, will play a fundamental role in explaining these phenomena. We also argue that population and market size can be endogenously determined by drugs through the impact of drugs over the mortality rate. Hence, these two effects reinforce each other, producing decrements in the mortality rate and increments in the stock of drugs over time.

We obtained the set of new molecular entities approved by the FDA during the second half of the the 20^{th} century and we decomposed the data in a panel of 15 therapeutic categories over time. Using this data, we tested our hypotheses using different econometric methods (FE, GLS, IV, Tobit). The results support the hypothesis and are consistent across methods.

The results indicate that an exogenous increase in market size increases initially the number of new drugs. It is notable how this effect is amplified through the feedback

*I received helpful comments from Gary Becker, Fabian Lange, Kevin Murphy, Tomas Philipson and Annette Vissing-Jorgensen. The usual disclaimer applies.

effect of drugs over the mortality rate. In the long run, the initial increase on drugs and market size are both amplified in 25 per cent.

1 Introduction

The sustained increase of expenditures in health care over the 20^{th} century brought the cost of health and its finance to the top of the policy agenda. The determinants of health expenditure is thus an important topic.

One of the factors that seems to affect health expenditure is technological change, e.g. new treatments. Newhouse (1992), using an accounting analysis, attributed large part of the increase in health expenditures -in the U.S. over the second half of the last century- to technological change. Cutler and McClellan (1996) studied the growth of expenditure on heart attack treatment and found that large part of the increase on expenditure was due to new technologies and their diffusions.

Technological change in the medical sector includes new procedures such as endoscopies, transplantations or renal dialysis but also advances on products such as new drugs. This paper will focus on this last type of technological change, e.g. new drugs. Drugs is an important item in the cost of health as they represent almost 10 per cent of total U.S. health expenditure in 2000. Further, prescription drugs is also a rapid growing item as it grew from 23.500 millions of 1983 dollars in 1991 to 42.700 millions of 1983 dollars in 2000 [1].

A direct measure of technological change in the drug sector is the introduction of new drugs. Data on introduction of drugs during the second half of the 20^{th} century can be

[1] source: the Centers for Medicare and Medicaid Services, http://www.hcfa.gov/stats/nhe-oact/

obtained from the U.S. Food and Drug Administration (FDA). Since the implementation of the 1938 Food, Drug and Cosmetic Act, the FDA must approve all new drugs before they might be available to the public. This property of the US law allows us to reconstruct the history of new drugs in the US health market. Figure 1 shows the evolution of new molecules approvals over the period 1940-1997. The series shows a sustained increased in new drugs over time, except during the period 1955-65. This unique change of trend during this period might be the result of changes in the legislation. In fact between 1938 and 1962, any drug seeking approval from the FDA needed to show that it was a safe drug while starting on 1962, an additional requirement for a new drug approval is to show its efficacy on its therapeutical treatment.

[Insert figure 1]

This paper will focus in explaining this observed trend on the introduction of new drugs. A novelty of the paper is that it proposes two main interactions that reinforce each other allowing continuous increases on the stock of drugs and continuous decrements on mortality rate. The first element playing a role is the relationship between the creation of new drugs and the size of the health market. A larger size of the health market is associated with a larger number of drugs that producers would like to have available for marketing purposes. In fact a larger market size, holding constant the number of drugs, should be associated with larger profits per drug, which provide incentives for new firms to enter the market throughout the creation of new drugs.

A second interaction proposed on the paper is a feedback effect of the stock of drugs over the mortality rate. Intuitively, as different drugs are available to the public, a larger number of diseases may be attacked and mortality rates might decrease. In this case market size is

positively affected because population size becomes larger. This second relationship produces a feedback effect that reinforces any initial increase on the number of drugs. For instance consider an exogenous increase on population, holding per capita income constant. Health market size will rise and there will be a larger introduction of drugs and thus a larger stock of drugs. This larger stock of drugs will provide a lower mortality rate that affects population and will increase the size of the health market. Hence, a virtuous circle or a multiplier effect in the creation of drugs will occur.

To address those effects, the paper presents a model that discusses the determinants of drugs' introductions. The model deals in one hand with households that purchase health goods (drugs) to extend the expected life span of their members. On another hand, we consider pharmaceutical firms that introduce new drugs into the market as result of a research and development (RND) process. Those firms decide the moment to introduce new drugs by evaluating economic incentives. We initially show that the health market size is an important determinant of drugs' introduction. Later we show that a larger stock of drugs is associated with a lower death likelihood and thus with a lower mortality rate.

A second characteristic of the paper is the empirical design here developed. To analyze the effect of the market size over the creation of new drugs, we examine a panel of 15 therapeutic categories of drugs over the period 1950-1997. We use different methods to disentangle the effect. First, we use the method of fixed effects (FE) to deal with unobserved heterogeneity among therapeutic categories of drugs and we obtain estimates using within-drug variation. We also provide estimations adding-up between-drug variation by using the GLS method. Later, we estimate using Tobit regressions to deal with the fact that our left hand side variable is censored at zero.

Those methods do not deal with the potential simultaneity that might exist between market size and drugs, since we postulate that the stock of drugs might affect mortality rates (and thus market size). To disentangle the effect of market size over the introduction of drugs, we need some instrument correlated with market size but uncorrelated with unobservable factors that affect the introduction of drugs. To accomplish this task, we construct expected market size by projecting population in a 10-year horizon. We use this instrument because expected market size should be correlated with observed market size (up to some forecast errors) but uncorrelated with new drugs, since projected mortality rates used on the construction of the index, does not include the information on new drugs. Using this instrument we provide additional estimates of the same methods used above.

To test the second hypothesis of the paper, e.g. the effect of the stock of drugs over mortality rates, we estimate a production function for mortality rates across causes of death. The production function depends on inputs and technology where inputs are approximated by health expenditure, and technology depends on the stock of drugs available in the health market. We provide estimations of GLS and FE methods. Then to address potential simultaneity on drugs, we first differentiate the data and we instrument drugs. We find that the effect of the stock of drugs is negative and significant.

The remainder of this paper is developed in the following way. Section 2 provides a review of contributions related with the principal topics of the paper while section 3 describes the theoretical setup of the paper. Section 4 shows that health market size is a main determinant of the number of drugs available in the health sector. Section 5 characterizes the evolution of the economy and it shows a virtuous circle on the health market that allows lower mortality rate and larger number of drugs over time. Section 6 describes the econometric approach of

the paper and it describes the data set used in this paper. Section 7 presents and discusses the results while section 8 concludes.

2 Literature Review

This paper links inventions on the pharmaceutical sector with population by emphasizing a simultaneity between market size and new drugs.

This relationship has not been largely explored in the literature. However, there is a recent contribution in the topic by Geoffard and Philipson (2002). They stressed these effects by analyzing goods for which the extent of consumption affects its duration. They argue that the feedback effect from larger longevity affect RND decisions through market size.

The literature does not provide empirical estimates of this simultaneous relationship between drugs and market size. However, there are contributions that examine separately (1) the determinants of RND on the pharmaceutical sector and (2) the effect of drugs over life expectancy. As those topics are treated separately in the literature, we initially provide a review of the contributions on the first topic. Later, we indicate the main results of the literature when analyzing the effect of drugs over mortality rates.

With the 1962 amendment to the "Food, Drug and Cosmetic Act", researchers found it necessary to discuss the determinants of inventions in this sector to determine the true impact of the amendment in the structure of pharmaceutical innovations.

Among the structural factors that affect research and development, the literature stresses market size, past cash flow of firms, and research productivity. Peltzman (1973) provided a simple model that explained the introduction of drugs as a function of lagged market size.

Using a time-series analysis over the period 1948-62 (annual data), he found a strong positive effect of market size over the introduction of drugs. In his analysis, the 1962 amendment would have had a significant and negative impact over drugs introduced after 1962. Vernon and Gusen (1974) related the introduction of new chemical entities (new drugs) with the size of the firm -rather than the size of the market- and they found that a larger firm would introduce, holding everything constant, more drugs.

Grabowski (1968) focused on explaining research and development of the American chemical, drug, and petroleum industries. He used variables (after-tax profits, number of patents per scientist, diversification index) that affect the expected returns from RND -rather than market size directly-. He found that these variables have a positive and significant impact over RND. Grabowski and Vernon (1981) emphasized the role of past cash flow as inputs on the process of RND in the pharmaceutical sector. They argued that the impact of the 1962 amendment had a dynamically negative effect on a firm's profits and RND. A more recent study is the one of Lichtenberg (1998a) about the allocation of publicly-funded biomedical research. He found that research funding should increase with disease incidence. Thus diseases affecting a larger number of individuals, which is a concept linked to market size, should have larger public research funds.

There is also some evidence on the effect of drugs over the mortality are and life expectancy. Lichtenberg (1998b) related the introduction of new drugs with an increase in life expectancy. Using cross-section data on diseases for two different periods (1970-80 and 1980-91), he found that the introduction of new drugs increased life expectancy by about 0.75-1.0 per cent per annum. Lichtenberg (2002) explained life expectancy by using a times-series analysis over the second half of the 20^{th} century in the U.S. The long run elasticity of longevity, with respect to

the number of new drugs approved, is significant and near 0.03. Lastly in Lichtenberg (2001), he analyzed the effects of drugs on mortality from rare diseases and HIV. New drugs, and especially drugs developed through the orphan drug act of 1983, show an important impact on reducing mortality from those diseases.

Thus the literature links inventions on the pharmaceutical sector with different measures of rate of return -including market size- and there is also some initial evidence of the positive impact of drugs over life expectancy. Notice that in general those studies (1) do not consider the interaction between drugs and population and (2) use only time-series evidence or cross-section evidence with a small data set. This paper will specifically link population and drugs in its theoretical section and it will provide evidence of those effects in its empirical section. This section uses a panel data on 15 therapeutic categories of drugs over the period 1950-1997 to provide evidence of the effect of market size in the introduction of drugs. It also uses instrumental variables to control the simultaneity problem as indicated above. When considering the effect of drugs over mortality rate, we use a similar panel to disentangle the effects.

3 The Environment

In this section we describe the theoretical setup used on the paper. In this economy, time is continuous. There is a representative household that maximizes its expected utility by extending the lifespan of their members -which will be assumed to depend on drug consumption. Pharmaceutical firms invent drugs and obtain the monopoly right to sell them. The problems of individuals and firms, plus the market clearing conditions of this economy are described

next.

3.1 The households

We describe now the problem of the representative household. The household has N_t members at time t. Each member of the household faces only two possible states: (1) being alive or (2) dead. If she is alive, she obtains an utility level equals to u_1 while if she is dead she gets u_0, where we assume both utility levels are constants with the property: $u_1 > u_0 = 0$. Let $\lambda(\widetilde{h_t})$ be the fraction of the household members that die, where $\widetilde{h_t}$ is the health level of a member of the household and the subscript t indicates time. This health level will depend on total health goods purchased and consumed by each individual. Also, there are $n_t N_t$ individuals born at t, where n_t is fertility rate. We will assume that fertility rate is constant:

$$Assumption \quad 1 : n_t = n, \forall t$$

The total flow of utility in the household at t is $u_1 N_t$, which is the utility per member alive times the size of the household. Hence, we can define the household's expected welfare function -U- at t=0 as:

$$U = \int_0^\infty u_1 N_t e^{-\rho t}\, dt = \int_0^\infty u_1 e^{-\rho t} e^{\int_0^t n_s - \lambda(\widetilde{h_s})\, ds}\, dt \tag{1}$$

Where ρ is the household's constant discount rate, $e^{\int_0^t \lambda(\widetilde{h_s})\, ds}$ is the survival density function and the level of population at time t=0 was normalized to one. Notice that the inclusion

of population in the setup is analogous to the inclusion of a non constant discount factor as in Becker and Mulligan (1997). Hence, the "modified" discount factor depends on the rate ρ and population growth rate. The basic properties of the utility function U will be $\lambda_h < 0$ and $\lambda_{hh} > 0$, where the second property is required to satisfy second order conditions [2].

The production function that determines $\widetilde{h_t}$ depends on two factors: (1) a larger expenditure on health, (2) new drugs (technologies). The first factor indicates that all things being equal, a larger expenditure on treatments should provide a better result on an individuals' health. The second factor indicates that new technologies might provide alternative solutions for disease not yet controlled or might provide advance solutions for diseases that already have some treatment. Mortality rates could also be affected by others factors -such as nutrition and/or health public policy-, however those effects will be omitted in this analysis.

To introduce these ideas into our setup, we will follow the approach of Spence (1976) and Dixit and Stiglitz (1977). They introduce symmetrical and concave preferences that produce a taste for variety on goods consumed. As in their case, health level will depend not only on the total quantity of health goods (drugs in our case) consumed but also on the number of different drugs consumed. To formalize the argument, let's assume that there are M_t drugs available at time t. As a matter of notation, each good will be indexed by i, where i $\in \{1, ..., M_t\}$ and let per capita quantity consumed of drug i at t be h_{it}. The total health level $\widetilde{h}$ will be specified as:

$$\widetilde{h_t} = \left[\sum_{i=0}^{M_t} (h_{it})^{\varepsilon} \right]^{\frac{1}{\varepsilon}} \tag{2}$$

[2] See mathematical appendix

Notice that this function implies that mortality rate will be negatively affected by per capita consumption of each drug and also by the number of drugs. When $\varepsilon = 1$, the CES function becomes total drug consumption, e.g. the sum of the consumption of each of the drugs. In that case, drugs are simply perfect substitutes between each other and we might obtain a solution where only one type of drugs is consumed. In practice, drugs with similar therapeutical use might be used as substitutes but drugs with different therapeutical cannot be considered as substitutes. Thus we will allow some degree of substitution but we will rule out extreme cases. To avoid such cases, we will assume $0 < \varepsilon < 1$. Ruling out the perfect substitutes and the leontief cases, we assure interior solutions for the consumption of each drug.

We will next discuss the budget constraint of the household. The timing of the problem is the following. At the beginning of each period, the household is endowed with some level of capital stock (assets), which is carried over from the previous period, K_t. Assets are used on a linear household's production function to obtain some physical output: y_t=BK_t, where y_t is physical output and B>0 is a constant parameter. The physical output can be stored and used as assets, which then can be carried over to the next period of time, or be sold by the household to obtain income. Once income is obtained, the household purchases drugs at the market price P_{it}, where P_{it} is measured in terms of physical goods. It should be noted that the capital stock depreciates at a rate of δ >0. Hence, the household budget constraint at time t is the following:

$$\dot{K} = BK_t - N_t \sum_{i=0}^{M_t} P_{it} h_{it} - K_t \delta \tag{3}$$

Notice that with the above budget constraint, we are multiplying per capita consumption of drug i by the size of the household to obtain the total health expenditure of the household on the i^{th} drug.

There is also a borrowing condition that must be imposed. This is the usual transversality condition that rules inefficient accumulation of capital stock. It indicates that at the end of the planning horizon of the household there would not be valuable assets left. To state the condition, let μ_t be the shadow price of household's assets at time t. The condition is:

$$\lim_{t\to\infty} K_t \mu_t = 0 \tag{4}$$

To sum up, a household chooses per capita purchases of each of the drugs available, $\{ h_{it}\}_{t=0,\ldots\infty}^{i=0,\ldots,M_t}$, to maximize (1) subject to (2)-(3)-(4), and the fact that h_{it} should be non negatives. In this problem, the household faces prices as well as the number of drugs available over time, M_t.

3.2 The pharmaceutical firms

The drugs purchased by the household are produced by pharmaceutical firms that must find economic incentives prior to introducing new drugs into the market. Thus the number of drugs, M_t, is endogenous. The firms engage in RND processes which provide inventions -new drugs. It is assumed that each firm produces only one drug. The economic incentives on the pharmaceutical sector are based on perpetual monopoly rights obtained to produce and sell the new drugs.

The timing for a pharmaceutical firm's problem is the following. Initially, a firm must decide if it will engage in developing a new product at a cost of η units of the physical good. This invention cost is paid completely during one period of time. There is certainty in the output of the RND process. As a result, a firm that spends η units of the physical good will obtain a new design. This design will be used to produce a drug that is not currently available on the market.

The production process for a firm with a new design is the following. Physical goods produced by a household are used as a unique input for the production of the drug. This input enters the production process with the only modification being its inclusion within the design. The result being the drug that is sold in the market. The material cost will remain for each subsequent period, while the use of the design for each subsequent period no longer has a cost. We will assume that the drug's production function is linear in relation to the input as in: $h_{it}=Dy_{it}^{d}$, where y_{it}^{d} is the amount of physical goods used as input on the production process of drug i at time t. The parameter D is a constant technology parameter and it satisfies $D>0$.

There is free entry into the pharmaceutical sector. For example, if the present value of profits for a firm i, V_t^i, is bigger than η, an infinite amount of resources will be devoted to the sector at time t. In the same way, if V_t^i is smaller than η, no resources will be devoted to the sector at all. As a result, V_t^i will be equal to η on equilibrium.

With this description, we are able to set up a problem that enables the firm to decide the moment of market entrance as well as the drug's unit price. It should be noted that once the firm enters into the market, they will need to reevaluate their unit price decision for each period of time.

Using the zero-profit condition within the pharmaceutical industry, we can state:

$$V_t^i = \int_t^{\infty} \{max_{P_{iz}}[P_{iz} - \frac{1}{D}]H_{iz}(P_{iz})\}e^{-\int_t^z r(s)ds} = \eta \tag{5}$$

Where $H_{iz}(P_{iz})$ is the aggregated demand for drug i and r(z) is the interest rate of the economy at time z. In the above zero-profit condition, the marginal cost of production is 1/D.

In order to characterize the price decision for the firm, we must obtain the current demand function faced by the firms. Notice that the household utility function is separable on the consumption of drugs over time. This property allows us to solve the problem for the household, conditional on having the total health expenditure. With that we may obtain the demand functions for each drug. Later we aggregate over individuals to obtain aggregated demand faced by the monopolist. With this information, we can solve the monopolist problem.

Therefore we can use:

$$max_{h_{it}} \left[\sum_{i=0}^{M_t}(h_{it})^{\varepsilon}\right]^{\frac{1}{\varepsilon}} \; s.t \; Eh_t = \sum_{i=0}^{M_t} P_{it}h_{it} \tag{6}$$

Where Eh_t is total health expenditure per capita at time t. By solving this problem, we arrive at the individual demand function for drug i:

$$h_{it} = \left[\frac{Eh_t}{\sum_{j=0}^{M_t}(P_{jt})^{\frac{\varepsilon}{\varepsilon-1}}}\right](P_{it})^{\frac{1}{\varepsilon-1}} \tag{7}$$

When the number of drugs -M_t- is large, the price decision is $P_{it} = \frac{1}{D\tilde{e}}, \forall$ i,t. Notice that this result allows us to conclude that the household will choose $h_{it} = h_{jt}, \forall i, j$ since health goods enter symmetrically on the utility function. These results are standard in the literature -see Barro and Sala-i-Martin (1995, pag. 231-233)- and they will be used later.

It should be noted that we must also determine the number of drugs over time, M_t. The second variable that characterizes the pharmaceutical sector will be analyzed later.

To completely describe the economy, the next subsection indicates the market clearing conditions that must hold on any equilibrium. Next we provide a definition of this equilibrium for our economy.

3.3 The equilibrium

In this economy, there are M_t+1 markets: M_t markets for drugs plus the physical good market. All these markets must clear. Once we impose the market clearing conditions and we satisfy the household and the firm's problem, we can define the equilibrium in this economy. Next we determine the market clearing conditions.

To satisfy the market clearing conditions on drugs, we impose that for any drug i, total demand must be equal to its supply. Hence the next set of conditions must hold:

$$h_{it} e^{-\int_0^t (\lambda(\widetilde{h_s}) - n_s) ds} = H_{it}, \qquad i = 1, ..., M_t \tag{8}$$

Where H_{it} is the total supply of health good i at time t. Hence, the right hand side of the condition is the supply of good i at time t, determined by the i's monopolist. The left

hand side is the total amount consumed by households, that can be decomposed on per capita health consumption of good i at time t, h_{it}, and population size, N_t.

In the same way, the market of the physical good must also clear. As indicated above, this good can be used as (1) input in the production of the health goods, as (2) asset to be carried to next period and as (3) investment on RND. Hence it must hold the following:

$$Y_t = \eta \dot{M}_t + \sum_{i=0}^{M_t} \frac{y_{it}^d}{D} + I_t \tag{9}$$

Where Y_t is total production of physical good and I_t is aggregated investment on assets (including depreciation). The dot indicates time differentiation; hence the first term on the right hand side indicates total investment on RND and the summation indicates the total amount of physical good used as inputs in the production of health firms. The equilibrium will be defined next.

Definition of equilibrium: The equilibrium of the economy consists of a set of households demand functions $\{h_{it}\}_{t=0...\infty}^{i=0...M_t}$, *a set of health prices* $\{P_{it}\}_{t=0...\infty}^{i=0...M_t}$, *a set of firms's input demands* $\{y_{it}^d\}_{t=0...\infty,}^{i=0...M_t}$ *and the evolution of the number of drugs* $\{M_t\}_{t=0...\infty}$, *such that:*

1. *Households solve their problems.*
2. *Pharmaceutical firms solve their problems.*
3. *Market clearing conditions hold.*

4 The role of market size

This section will focus on the determinants of drug inventions. We will show that market size determine the introduction of new drugs. Market size will depend on population and per capita income that affects per capita demand for drugs. Thus any change on these components will affect RND. The argument follows the pharmaceutical firm's decision to introduce a new drug. Consider an exogenous increase on market size -due to a larger population or per capita income. As a result, aggregated demand for pharmaceutical goods will raise and incumbent firms will have positive profits, thus $V_t^i > \eta$ for any firm i at time t. Those positive profits provide incentives for new firms to enter to the drug market (by the zero-profit condition), and therefore new drugs become available.

To clarify the point notice that since consumers purchase the same amount of each health good, the zero-profit condition of pharmaceutical firms can be written as:

$$V_t^i = \int_t^{\infty} (\frac{1-\varepsilon}{D\varepsilon})(\frac{H_z}{M_z}) e^{-\int_t^z r(s)ds} = \eta \tag{10}$$

where H_t is defined as $\sum_{i=0}^{M_t} H_{it}$, the total quantity of drugs purchased by households at the current prices while $(1-\varepsilon)/D\varepsilon$ is the markup obtained by each firm. We should differentiate this zero-profit condition with respect to time -using the rule for integral differentiation. This yields:

$$(\frac{1-\varepsilon}{D\varepsilon})\frac{H_t}{M_t} = r_t\eta \tag{11}$$

This is an arbitrage condition of an entrant firm into the pharmaceutical sector -thus an arbitrage condition to introduce a new drug. It states that the firm is willing to postpone its entry to the market for a period of time if the loss in marginal benefit equals the gain of avoiding the RND cost for one period. The left hand side is the gain of producing the good, as (1-ε)/Dε is the markup and H_t/M$_t$ is the quantity sold by the firm if its operates. (each firm on the market has the same share since they charge the same price and face the same demand function). The right hand side is the financial gain of postponing the entry.

When the interest rate is stationary over time -we will show below that this is the case-, the right hand side of the arbitrage condition is constant and so must the left hand side.

Notice that using market clearing conditions on the drug market, the aggregated amount of drugs supplied by pharmaceutical firms can be written as:

$$H_t = \sum_{i=0}^{M_t} h_{it} N_t = h_t N_t$$

where $h_t = \sum_{i=0}^{M_t} h_{it}$ is total per capita consumption of drugs. The condition indicates that the total amount of drugs sold by the industry -H_t-, which is a measure of market size, can be decomposed on (1) total per capita consumption of drugs and (2) population. This simple decomposition provides an interesting conclusion in relation with the introduction of drugs.

The arbitrage condition implies that a larger market size, due to a larger population size or a larger per capita expenditure on drugs, is associated with the introduction of new drugs into the drug market.

So far we have shown that a larger market size is associated with more drugs. It is of

great importance to notice that there exists a feedback effect though. As drugs decrease the mortality rate, there will be an increase in population growth and thus market size. Therefore we have a mutual dependency that reinforces endogenously the creation of new drugs through sustained decrements on the mortality rate while providing for the increase of population. Next section will describe this relationship.

5 The behavior of the economy

This section will describe the behavior of the economy over time. We will show that mortality rate and the stock of drugs have opposite and sustained trends, as the stock of drugs rises the mortality rate decreases continuously over time.

To characterize the economy, the following assumption will be stated:

$$Assumption \quad 2 : n < \rho < B - \delta$$

We stated this assumption because it assures the utility function to be bounded and the transversality condition satisfied - see mathematical appendix.

We will analyze first the dynamics of the household. Notice that the household's problem can be written in the following Hamiltonian:

$$\mathcal{H}(K_t, \mu_t) = u_1 e^{-\rho t} e^{\int_0^t n_s - \lambda(M_s^{(\frac{1-\varepsilon}{\varepsilon})} h_s) ds} + \mu_t[(B-\delta)K_t - N_t P h_t]$$

Where the above Hamiltonian replaces $h_t = \sum_{i=0}^{M_t} h_{it}$. We work with total per capita amount of drugs purchased, h_t, rather than with the amount purchased per drug, h_{it}, because the utility function is symmetrical on drugs, and prices are the same for each drug. Thus the first order conditions are the same for any drug. Hence we will condense the information on a single first order condition. The associated first order condition is:

$$-\lambda_h M_t^{(\frac{1-\varepsilon}{\varepsilon})} u_1 e^{-\rho t} e^{\int_0^t n_s - \lambda(M_s^{(\frac{1-\varepsilon}{\varepsilon})} h_s) ds} = \mu_t N_t P \tag{12}$$

The left hand side is the marginal benefit of an additional unit of per capita drug consumed while the right hand side is its associated marginal cost. Notice that $-\lambda_h M_t^{(\frac{1-\varepsilon}{\varepsilon})}$ is the change on mortality rate when we increase the consumption of drugs. Thus the left hand side is a total change on utility. The right hand side indicates that the cost depends on the price of drugs P, the size of household -the household spends the same per capita amount on each of its members- and on the shadow price of capital -μ_t-.

A second condition characterizing the household's problem is:

$$\frac{\dot{\mu}}{\mu} = -r_t = -(B - \delta) \tag{13}$$

This condition is an arbitrage condition on capital stock. It indicates that the capital gain of holding a unit of capital, $\frac{\dot{\mu}}{\mu}$, plus its rental must be equal to zero. If the capital gain plus rental rate of capital stock was positive (negative) there would be incentives to accumulate a larger (smaller) stock of capital. As such this condition determines the expansion path

of capital over time. Notice that interest rate is constant over time and depends on the parameter of the model.

We may obtain some additional information by differentiating equation (12) with respect to time and using equation (13). This yields:

$$\frac{\dot{h}}{h} = \frac{r_t - \rho}{-\sigma_\lambda} + (\frac{(1+\sigma_\lambda)(\frac{1-\varepsilon}{\varepsilon})}{-\sigma_\lambda})\frac{\dot{M}}{M} \tag{14}$$

Where σ_λ is defined as $\sigma_\lambda = (\frac{\lambda_{hh}}{\lambda_h} M_t^{(\frac{1-\varepsilon}{\varepsilon})} h_t) < 0$ by second order conditions. This coefficient, σ_λ, is a coefficient of risk aversion on health as it measures concavity on the survival density function.

Equation (14) indicates that the evolution of per capita drug consumption depends on two components, (1) the difference between interest rate and discount factor and (2) the growth rate of the stock of drugs.

If the rental rate is bigger than ρ, individuals are willing to postpone current expenditure on drugs to accumulate larger capital stock. In that case, future resources and future per capita drug expenditure rises.

The effect of the growth rate of drugs depends on the the sign of $(1 + \sigma_\lambda)$. Intuitively, there are two effects when the growth rate of drugs rises: (1) an income and (2) a substitution effect. A larger growth rate of drugs is associated with a larger future stock of drugs. As the future number of drugs rises, it is easier to attain a given level of mortality rate. We may reallocate resources away from future drug expenditure (this is the income effect). We do have a second effect though. As there is a large stock of drugs in the future, there are more

incentives to increase future drug expenditure because its return -effect over the mortality rate- is larger in the future (this is the substitution effect). We will assume that $\sigma_\lambda < -1$ and thus per capita health expenditure, h_t, decreases if the stock of drugs rises.

We will next characterize the evolution of drugs. From the arbitrage condition that characterizes the entry decisions of firms into the drug market -equation (11)-, we know that the number of drugs will follow the evolution of market size. Thus to determine the evolution of M_t over time we will focus on the dynamics of market size. The above market size is defined as:

$$H_t = h_t N_t = h_t e^{-\int_0^t (\lambda(\widetilde{h_s}) - n_s) ds} \tag{15}$$

Differentiating this expression over time we get a first approximation for the growth rate in H_t and thus on M_t:

$$\frac{\dot{H_t}}{H_t} = \frac{\dot{h_t}}{h_t} + n_t - \lambda(\widetilde{h_t}) = \frac{\dot{M_t}}{M_t} \tag{16}$$

Notice that using equations (14) and (16), we will obtain the evolution of drugs over time. This yields:

$$\frac{\dot{M}}{M} = (\frac{\varepsilon}{\varepsilon - (1+\sigma_\lambda)})[r_t - \rho] + (\frac{-\sigma_\lambda \varepsilon}{\varepsilon - (1+\sigma_\lambda)})[n - \lambda] \tag{17}$$

Where $\varepsilon - (1 + \sigma_\lambda) > 0$ and $\lambda = \lambda(M_t^{\frac{1-\varepsilon}{\varepsilon}} h_t)$. This equation shows that the growth

rate of drugs depends on two components: (1) the difference between rental rate and time preferences[3] and (2) population growth rate. In fact, if rental rate is larger than the discount factor, individuals are willing to accumulate more resources, that can be spent in the future. Therefore future demand for health at the per capita level rises. The second component indicates that a larger population growth rate is associated with a larger increase on the drug market size. This provides incentives for the firms to engage in RND and provide more drugs.

We may also characterize the evolution of mortality rate over time. Using equations (14), (16) and (17), we get:

$$\frac{\dot{\lambda}}{\lambda} = (\frac{\eta_\lambda}{\varepsilon - (1+\sigma_\lambda)})[r_t - \rho] - (\frac{\eta_\lambda(1+\sigma_\lambda)(1-\varepsilon)}{\varepsilon - (1+\sigma_\lambda)})[n - \lambda] \tag{18}$$

Where $\eta_\lambda = (\frac{\lambda_h}{\lambda} M_t^{(\frac{1-\varepsilon}{\varepsilon})} h_t) < 0$ is the elasticity of mortality rate with respect to an increase on $\widetilde{h_t}$.

The equation indicates that the mortality rate is negatively affected by population growth rate and by the difference between rental rate and the constant discount factor, ρ. The intuition is the following. Consider first the case of positive population growth rate. In that case, the economy has a drug market size growing over time and therefore the stock of drugs rises continuously. This continuous increase in the stock of drugs produces lower mortality rates. The effect of a larger rental rate of the economy compared to ρ follows the same argument. The intuition in this case is that individuals are willing to postpone current drug consumption to accumulate resources that are spent in the future. As a result, there is the

[3]Which is positive by assumption 2

continuous demand increase per capita for drugs. This causes the effect over market size, and the introduction of new drugs.

Notice that equations (17) and (18) are a system of two equations that describe the evolution of drugs and mortality rate over time. We will next provide an example of the evolution of drugs and the mortality rate. This example does not intend to calibrate the economy but only to provide a feeling of the behavior of the variables. Hence, we will choose some parameters that only satisfy the restrictions imposed above, but they do not need to replicate any observation from the economy.

We will assume that mortality rate follows a simple constant elasticity function $\lambda = \frac{(M_t^{\frac{1-\varepsilon}{\varepsilon}} h_t)^{\sigma}}{\sigma}$, where $\sigma = -0.5$ and thus $\sigma_\lambda = -1.5, \eta_\sigma = -0.5$. Further we will assume that $\varepsilon = 0.5, r_t - \delta = 0.04, \rho = 0.01, n = 0.05$. The initial level of mortality rate is set equal to the exogenous fertility rate while the initial level of drugs is fixed at an arbitrary level, $M_0 > 0$. Figure 2 characterizes the evolution of the economy under those assumptions.

[Insert figure 2]

The figure shows sustained trends in both variables as we expected. The number of drugs grow at an exponential rate while mortality rate presents smaller decrements over time.

6 The data

We next provide empirical evidence to the effects stressed above: (1) the impact of market size over the creation of drugs and (2) the effect of drugs over mortality rates.

To disentangle these effects, we use information on drugs from 15 different therapeutic categories over time. We also construct alternative measures of market size per therapeu-

tic category by approximating total purchasing power of individuals buying drugs. We are weighting different measures of purchasing power by age using prevalence rates. Additionally, we obtain data on government funds used on the RND process of the pharmaceutical sector. This last variable is used as an additional control on the equation determining the effect of market size over drug creation. This section describes this data.

6.1 Drugs

The data on drugs was obtained from the FDA by using a freedom of information request. We obtained a list of all new drugs approved since 1939. Each record is composed by the trade name of the drug, the approval date, the chemical type, and the generic name of the drug among other possible categories.

The chemical type of a drug has 7 possible classifications, which are:

1. *New molecular entity,* active ingredient that has never been marketed in the U.S.

2. *New derivative,* a chemical derived from an active ingredient already marketed

3. *New formulation,* a new dosage or new formulation of an active ingredient already marketed

4. *New combination,* a drug that contains two or more compounds, the combination of which has not been marketed together in a product

5. *Already marketed product but a new manufacturer*

6. *Already marketed product, but a new use*

7. *Already marketed legally without an FDA approval*

We will follow the empirical literature and focus on new molecular entities (NME) only. In fact, the rest of chemical types correspond to drugs that were derived from molecular entities

already on the market. Hence we will not classify them as new drugs. We found 1135 NME approved between 1939 and 1997. These are going to be used in our analysis.

To construct the panel of drugs, we use its generic name. This information allows us to determine its therapeutical use. Therapeutical use indicates the type of disease the drug deals with. The therapeutic use was determined by consulting the 9^{th} edition of the Drug Information Handbook (DIH) published by Lexi-Comp and the American Pharmaceutical Association. This DIH is similar to a pharmaceutical dictionary as it provides an alphabetic list of drugs in the market by generic name (U.S. adopted name). Each drug listed on the DIH has information about its therapeutical category, its use, its contraindications, and adverse reactions among other fields.

We have classified the drugs into 15 different categories (column 1 of table 1) . We chose these categories based on the 1995 National Drug Classification (NDC). Among these categories we find antidotes, hematologic drugs, cardiovascular-renal drugs, etc..

[Insert table 1]

To classify the drugs over time, we used the approval date on each record to obtain the year the drug was approved for marketing purposes.

Using this information, we obtained a list of drugs classified in 15 different therapeutic categories over the period of 1939 to 1997.

6.2 Mortality rates

We constructed a series on mortality rates for each of the 15 therapeutic categories. To do so, we matched each of these therapeutic categories to a set of causes of death. We used the 9^{th} version of the International Classification of Diseases (ICD-9) to determine the matching

process between death and drugs. This classification ranges from 1 to 999, where each number is associated with a cause of death. This ICD-9 classification allows us to match each death with one of the drug categories. To see the way we match deaths and drugs, refer to table 1.

To construct the mortality series, we use the U.S. National Mortality Detail Files (NMDF) publicly available from the Inter-University Consortium for Political and Social Research (ICPSR) over the period 1968-1997. The NMDFs have a record per each death occurred on the U.S. during each year. The record includes the cause of death, which is determined by the ICD-9. Using this information, we are able to construct mortality series by therapeutic category from 1968 to 1997.

6.3 Market size

To figure out the size of the market for each of the drug categories, we construct two alternative measures of market size. Each measure will construct market size by using population and individuals' income. We implement this strategy because a larger population is associated with a larger market size. Also we use per capita income because a larger per capita income allows a larger expenditure on drugs at the individual level. Thus we link market size with purchasing power of the population in the economy.

The two measures differ on the definition of income. The first measure uses current median income of individuals while the second uses an index of permanent income we develop later.

Another qualification with respect to the construction of market size is that we obtained data on population and income by age-groups over time. We use this strategy because individuals might change their consumption of drugs during their lifecycles. In fact, we expect that older individuals will spend more on drugs and medical procedures than younger individuals,

everything else being equal. As a result we will give more importance to older individuals when constructing market size.

From the U.S statistical abstract, we obtained data on the populations of different age-groups since 1950 to 1997. The groups in this paper are individuals aged 25 to 34, 35 to 44, 45 to 54, 55 to 64, and 65 and older. In addition to population, we obtained data on the U.S. median income for people in each of these groups at 1997 CPI adjusted dollars from the Current Population Reports of the Census. By multiplying population and median income at each age-group, we obtained the purchasing power in each respective age-group.

To construct the size of the market, we will add-up the purchasing power of those groups by using appropriated weights for each of them. The obvious weights to be used are prevalence rates. A group with larger prevalence rate in a given disease, has relatively more individuals affected with the disease and should consume more treatments, relative to groups with lower prevalence rates.

We obtained a proxy for prevalence rates by using the National Mortality Detail Files. In fact, each record on the NMDF provides the age of the individual that died. This information allows us to classify each death on one of our age groups. Next, to determine the prevalence rate per age-group for a given disease, we use the set of individuals dying of a specific disease. We determine the fraction of individuals dying per age-group and we divide by the total number of death as in:

$$\varpi_{it}^{J} = \frac{\sum\limits_{j \in \{J\}} j_{it}}{\sum\limits_{j} j_{it}} \tag{19}$$

Where ϖ_{it}^{J} is the weight -proxy for prevalence rate- of age-group J on disease i at time t and j_{it} is an indicator function equal to one if the record indicates that the individual died from disease type i at t and zero otherwise.

Consider the following example of prevalence rates for hematologic drugs. These drugs are related directly with diseases of the blood, which are the ones encoded between 280 and 290 on the ICD-9 code. Thus the prevalence rate of individuals aged 65 and older is defined as the total number of individuals aged 65 and older who died of blood diseases, over the total number of individual who died of the same diseases.

Using this information, we define a first series of market size per drug-category i at time t as:

$$MKS_{it} = \sum_{J} \varpi_{it}^{J} pop_{it}^{J} y_{it}^{J} \tag{20}$$

Where MKS_{it} is market size per therapeutic category over time while pop_{it}^{J}, y_{it}^{J} are total population and median individual income of age-group J at t.

The above index measures market size using current income. We develop next a second measure that uses permanent income instead. This measure follows the same basic construction as the one shown in equation (21), but uses permanent income rather than current income.

We define permanent income for an individual born at time t as:

$$y_t^p = \frac{1}{T} E_t[\sum_{z=t}^{T+t} R^z y_z] \tag{21}$$

Where y_t^p, E_t indicate permanent income and expectation at t respectively while $R = \frac{1}{1+r}$ -r is interest rate- an d y_z is current income. The date t is the date the individual enters to the labor market while T is the number of years the individual works and obtains income. We set T=40 years.

As in Flavin (1981) and Deaton (1992), we assume that income follows an autoregressive process, as in $y_t = \alpha y_{t-1} + \epsilon_t$ where ϵ_t is a zero-mean error term [4]. This assumption yields:

$$y_t^p = y_0 \alpha^t [\frac{1-(\alpha R)^{T+1}}{1-\alpha R}] \tag{22}$$

We use this expression to approximate permanent income. We estimated α using per capita income annual data over the period 1929 to 1999 obtained from the U.S. Bureau of Economic Analysis. We construct a series of permanent income over the period 1929 to 1997 by using the point estimate, $\alpha = 1.018$, setting r=0.05 and $y_0 = 1$ in 1929.

Using permanent income, we construct an alternative measure of market size:

$$\widetilde{MKS}_{it} = \sum_J \varpi_{it}^J pop_{it}^J y_{it}^{pJ} \tag{23}$$

Where y_{it}^{pJ} is permanent income of age-group J at t.

[4] In the literature on consumption and permanent income, there are different autoregressive processes. These processes depend on some assumption about the stationarity of income. Deaton (1992) provides a discussion about the change on permanent income and consumption if the income process is difference-stationary or trend-stationary. Here, I will follow Flavin (1981) assuming an AR process on income.

6.4 Government grants on pharmaceutical research

A variable that may have influence on RND is government grants for medical research. We obtain data on government grants for medical research from the National Health Institutes (NIH) almanac over the period 1948 to 1997. The NIH is composed by different institutes which provides funds for private research within the pharmaceutical sector. Among them, we find the National Cancer Institute (NCI), the National Hearth, Lung and Blood Institute (NHLBI), the National Institute of Mental Health (NIMH), etc...

We compute government expenditure in each of the therapeutic categories by mapping expenditure on a specific institute with a specific therapeutic category. The way we mapped the government expenditures can be seen on table 2. In the table, there are some centers whose grants were divided between diseases because they cannot be directly mapped with a unique disease. An example is the case of the NHLBI whose grants were divided among hematologic, cardiovascular-renal and respiratory tract drugs.

[Insert table 2]

6.5 Expenditure on hospital bed per therapeutic category

When explaining mortality rates across therapeutic categories, we will have as a control the expenditure on medical treatments. We will assume that mortality rates are determined by a production function which depends on technology (number of drugs) and inputs (expenditure on medical treatments).

To approximate expenditure in medical treatments by therapeutical category, we obtained data on total hospital beds use at national level per annum. We compute the data by therapeutic category over the period 1980 to 1997 from the National Hospital Discharge Survey

(NHDS).

Next, we construct real expenditure on hospital beds per therapeutic category. We multiply total hospital beds per therapeutic category by the price index "hospital and related services" (obtained from the bureau of labor statistics) and divide it by CPI. This variable will be used as a proxy variable for real health expenditure per therapeutic category.

6.6 Some initial evidence of the effect of market size

Figures 3 and 4 show the evolution of new molecular entities approved by FDA compared with the growth rate of the population of individuals aged 45 to 64 years old, and 65 years and older in the US over the period 1955-1997. The figures show a very similar evolution of population and drugs approved over time. As we expected, there is an increase in market size due to a larger population as associated with the introduction of new drugs by pharmaceutical firms.

[Insert figures 3 and 4]

Even when the evolution of these series are quite similar, some qualifications seem to be in place. First, the aggregated time-series shown above might not be the most relevant measure of drug inventions when related to market size. Drugs might have different therapeutical uses and thus different drugs might be related to consumers at different stages of their lifecycle. Thus drugs used intensively by elderly individuals, such as Alzheimer's drugs, will have a different market size compared to ophthalmic, otologic or skin related drugs.

To expand on this concept, we will next focus on analyzing the relationship between market size and drugs across therapeutic categories. Figures 5 to 7 plot the number of drugs (vertical axis) versus market size (using current income) measured in thousands of billions of

dollars (horizontal axis) for the therapeutic categories considered on this paper. The figures show a clear positive association between market size and number of drugs.

[Insert figures 5 to 7]

Even when figures 5 and 7 present a clear association between drugs and market size, this association might be the result of simple spurious correlation between series measured in levels. We would rather focus on the relation of the flow of drugs and market size (and other sources of demand such as government expenditure).

Table 3 reports summary statistics of the data. The table shows that there exists a large variation on the average creation of drugs across therapeutic categories. The table also shows that therapeutic categories with a larger creation of drugs are associated with a larger government expenditure on research grants. This is the case of the National Cancer Institute which is related with oncolytic drugs, the National Institute of Mental Health or the National Health, Lungs and Blood Institute which are related with the central nervous system and cardiovascular-renal drugs respectively. Conversely, therapeutic categories presenting lower creation of drugs present lower government expenditure on research. This is the case of the National Institute of Deafness and Other Communications Disorders or the National Institute of Arthritis, Musculoskeletal and Skin Disease.

[Insert table 3]

Figures 8 to 10 present plots of 10-years moving averages of flow of drugs and market size per therapeutic categories. We use these moving averages to emphasize long run trends in the data. A positive relationship between the creation of drugs and the size of the market can be observed. The relationship varies across therapeutic categories being clearly stronger

in neurologic, cardiovascular-renal, nutrients, respiratory and immunologic drugs. We find three exceptions: Ophthalmic, pain relief and hormone drugs. These do not present a clear relationship with market size. However, while hormone drugs present a smaller market size yet receive a larger government expenditure on research compared to other therapeutic drugs. Hence in this last case, we may argue that the more relevant measure of demand might be government expenditure. We can infer that the considerable creation of hormonal drugs can be explained by government grants as oppose to a private market size effect.

[Insert figures 8 to 10]

A similar situation is shown on table 4. This table presents market size and flow of drugs across therapeutic categories over four different decades.

[Insert table 4]

Similarly to figures 8-10, during the eighties and nineties market size increased as did the creation of drugs, with the exception of the drugs named above.

This analysis has focused on market size using current income. When we use permanent income similar results are obtained. When market size is using permanent income, it has a smoother evolution in comparison to the current income case, but the long run trends are similar (the correlation between the two measures of market size is 0.93).

Next section will provide more evidence and will test formally the predictions of this paper.

7 The empirical strategy and the results

7.1 The effect of market size

To test the effect of market size over the introduction of drugs, we follow equation (11) and we hypothesize a linear relationship between a firm's desired stock of drugs and market size. We also include additional control variables, as in:

$$SD_{it}^{*} = \alpha_i + \gamma_t + \alpha_1 MKS_{it}^{*} + \alpha_2 SD_{it-1} + \alpha_3 Gov_{it} + \alpha_4 DLEG_{it} \tag{24}$$

Where i indexes drug categories and t indexes time. The variable SD_{it}^{*} denotes a firms' desired stock of drugs while MKS_{it}^{*}, SD_{it-1}, Gov_{it} denote the market size of drugs, the lagged stock of drugs and government expenditures on drugs' research. The variable DLEG_t is an indicator function equal to one if the year is 1962 or later and it is equal to zero otherwise. α_i and γ_t are therapeutic fixed effects and time fixed effects, respectively.

The indicator function DLEG_t was included as a way of measuring the change within the legislation which occurred in 1962. In addition to the safety requirements of the pre-1962 period, the 1962 legislation requires the demonstration of efficiency of a new drug introduced into the market. We also included the lagged stock of drugs as a measure of knowledge. We expect a positive effect of knowledge over the creation of drugs and over the desired stock of drugs. In addition, we include government expenditure to measure government demand for drugs. The expected signs are $\alpha_1 > 0, \alpha_2 > 0, \alpha_3 > 0, \alpha_4 < 0$.

The flow of drugs can be defined as the change on the stock of drugs as in:

$$FD_{it} = SD_{it} - SD_{it-1}$$

Hence, replacing above yields:

$$FD_{it} = \alpha_i + \gamma_t + \alpha_1 MKS^*_{it} + \widetilde{\alpha_2} SD_{it-1} + \alpha_3 Gov_{it} + \alpha_4 DLEG_{it} + u_{it} \tag{25}$$

Where FD_{it} is the flow of drugs of ith therapeutic category at time t, $\widetilde{\alpha_2} = (\alpha_2 - 1)$ and u_{it} is a random shock that measure the difference between the observed stock of drugs, SD_{it}, and the desired stock of drugs, SD^*_{it}. The variables flow of drugs, stock of drugs and government expenditures have some values equal to zero while market size has only positive values. Thus we will take natural log in the case of market size while using the rest of the variables in levels.

Equation (25) will be estimated by different methods allowing us to identify the parameter of interests. First, we use within drugs information to disentangle the parameter of interest through the fixed effect method. Second, we add-up between drugs variation by using the GLS method - this method is a weighted average of the fixed effect and the between estimator. Later, we provide estimates of a Tobit regression to address a potential problem of censoring in the flow of drug data, as 298 of the 720 observations over the period 1950-1997 present a value equal to zero. To address potential simultaneity between drugs and market size, we construct a series of expected market size and we report new estimations for the methods described above, using this variable as an instrument.

7.2 The Instrument

Before reporting the results, we will explain the construction of the instrument used to break some potential simultaneity between new drugs and market size. Later, we will provide the results using direct estimation under the three methods and also using the instrument.

The instrumental variable procedure requires an instrument correlated with market size but uncorrelated with the flow of drugs, except through the variables that are included in the flow of drugs' equation. As instrument we will use expected market size which will be constructed by using forecasted population, where forecasted population depends on expected mortality rate.

Since our definition of market size depends on population by age, let's explain the way we forecast population at time t for a given age a, Pop_t^a. Let's take population at time t-j of age a-j, Pop_{t-j}^{a-j}, where j>0. These individuals and their mortality rate during the next j periods, d, will determine Pop_t^a, as in $Pop_{t-j}^{a-j}(1-d) = Pop_t^a$. It should be noticed that the flow of new drugs between t-j and t might affect mortality rate, d. This is the potential simultaneity problem. Rather than use the effective mortality rate, d, we will use d^*, where d^* is the expected fraction of individuals dying in the next j periods -expected mortality rate. The characteristic of d^* is that it uses information available until t-j. Thus information on new drugs invented between t-j and t is not included when constructing d^*.

We will define expected population for this group of individuals at time t as $Pop_{t-j}^{a-j}(1-d^*) = Pop_t^{a,*}$. This population, $\text{Pop}_t^{a,*}$, should be the one observed in absence of any shock that alters mortality rate. However, the observed mortality rate is altered by new drugs introduced to the market. This expected population is then uncorrelated to new drugs and it will be used on the construction of our instrument.

To construct expected population size, we use the life-tables published in the U.S. statistical abstract. These life tables provide expected mortality rates by age which are constructed by using current population and current death rates. The procedure to construct life tables uses death of individuals aged 1 to 84, obtained from the National Mortality Detail Files, while in the case of individuals aged 85 and older, mortality rates are constructed by using medicare data on mortality rates of their affiliates. -see Anderson and DeTurk (2002). We project those mortality rates into a 10-years horizon and we construct a 10-years forecast of the population for different age groups. Thus we define Pop^*_{jt}=$\text{Pop}_{j(t-10)} * (1 - d^*)$, where d^* is the expected mortality rate in a 10-years horizon.

We will construct expected market size as in:

$$EMK_{it} = \sum_j \varpi^i_{jt} Pop^*_{jt} y_{jt} \tag{26}$$

This construction is analogous to the construction of market size developed above -equation (20)- but we replace population by expected population, Pop^*_{jt}. Expected market size is uncorrelated with the flow of new drugs -except through variables that are included on the flow of drugs' equation- as argued above, but also this measure must be highly correlated with effective market size, as the only deviation in the construction of expected market size compared to effective market size, is the use of d^* instead of effective mortality rate, d. Table 6 presents the result of running market size on expected market size using FE and GLS methods, and controlling by time effects. There a significant and positive relationship between the variables and expected market size is clearly a much stronger instrument.

[Insert table 6]

7.3 The Results

We will now analyze the results obtained when estimating equation (25) by different methods. Tables 7a and 7b present the results.

The first three columns of tables 7a and 7b are the results of estimations using no instrument. Table 7a reports results using market size defined by current income while table 7b reports results for the permanent income case. The coefficient of the initial stock of drugs is strongly significant over the different estimations with a range of values between 0.03 and 0.1. These values are associated with elasticities -evaluated at the means of both variables- ranging from 0.7 to 2.4[5] indicating that accumulated knowledge would positively affect the creation of new drugs.

The effect of government research grants is also positive and significant. Evaluating at the mean of variables as above, we obtain elasticities of government expenditure ranging from 0.14 to 0.54. The effect of market size is positive in all the cases, as we expected, and strongly significant in five of the six cases. The elasticity of the flow of drugs with respect to market size is on the range 0.24 - 2.21[6]. The FE and tobit methods provide strong and significative estimates of the market size effect. Though using the between-drugs variations seems to diminish this effect (see GLS estimations, which include the between-drugs variation). This effect might be due to the potential simultaneity between market size and drugs. Thus we will next address this problem by instrumenting market size.

[5]The mean flow of drugs and the mean stock of drugs in our sample are 1.33 and 24.06 respectively
[6]Where we evaluate again at the mean flow of drugs

[Insert tables 7a and 7b]

Columns 4 to 6 of table 7a and 7b present the results when we use the instrument. The range of values for the coefficient of market size is much smaller than before and in fact the point elasticity ranges between 0.77 and 2.07 (those values are concentrated around 1.5). Further, the six cases are strongly significant. The fact that the elasticity belongs to a more compact range of values and that the GLS case also provides a significant result for market size indicates that any potential bias due to simultaneity is diminished as we use the instrument. The coefficients of government expenditure and lagged stock of drugs remains strongly significant in all cases and in similar ranges to the above case.

7.4 The effect of drugs over mortality rate

Next, we will estimate the feedback effect of drugs on mortality rate and thus on market size. To determine the effect of drugs over mortality rate, by using a linear version of the mortality rate function, $\lambda(M_t^{(\frac{1-\varepsilon}{\varepsilon})}h_t)$ - see section 2. We can assume that mortality rate for the i^{th} therapeutic category over time is determined by:

$$\lambda_{it} = \mu_i + \eta_t + \gamma_1 SD_{it} + \gamma_2 h_{it} + \gamma Z_{it} + \epsilon_{it} \tag{27}$$

Where λ_{it} is mortality rate, SD_{it} is the number of drugs available to public purchase, h_{it} is total health expenditure and Z_{it} is a set of additional control variables that might affect mortality rates. All these variables are measured per therapeutic category and time period. Lastly, μ_i and η_t are therapeutic fixed effects and time fixed effects respectively while ϵ_{it} is a

random shock. The expected signs are $\gamma_1 < 0, \gamma_2 < 0$.

This specification assumes that the mortality rate is determined by a production function that is dependent on technology (drugs in our case), inputs (health expenditure) and some additional variables that might shift the production function.

As additional control variables we will include year dummies, plus some demographic information such as the prevalence rates of disease i on males, blacks, whites and married individuals as well as the average age of individuals affected by disease i. We use the fraction of male individuals attending a hospital due to disease i as proxy variable for prevalence rate among men. Analogous proxies variables were constructed for white, black and married individuals. In addition, we use the average age of individuals attending a hospital due to disease i as a proxy for the average age of individuals affected by disease i. This data was obtained from the National Hospital Discharge Survey.

Equation (27) will be estimated by FE and GLS methods. We initially report results for the mortality rate equation using only the stock of drugs and year dummies -we omit h_{it}, Z_{it}. We follow this strategy as it allows us to report results over the period 1968-1997. When we include the measure of expenditure per therapeutic category, we can report results only over the period 1980-1997. We use three different left hand side variables: (1) overall mortality rate, (2) mortality rate of individuals aged 45 to 64 and (3) mortality rate of individuals aged 65 and older. Those variables are measured as number of dead individuals per thousand of inhabitants and they are reported in table 8a and 8b.

[Insert tables 8a and 8b]

The results in both estimation methods show a negative and significative impact of drugs over mortality rates, as we expected.

This preliminary results show that the effect of the stock of drugs over mortality rate measured as death per thousands of individuals is approximately equal to -0.01. Thus an increase of 10 per cent on the stock of new molecular entities (an increase of almost 100 NME) would produce a decrease of 1 point in mortality rate per thousand of individuals, bringing mortality rate from 6.4 per thousand on individuals (1997 level in our sample) to 5.4. Also the effect of the stock of drugs over mortality rates for individuals aged 65 years and older (coefficient approximately equal to -0.1) indicates that a 10 per cent increase on the stock of drugs would reduce the current mortality rate of this group from 40 per thousands -its 1997 level on our sample- to 30 per thousands individuals.

There are some other results that we will comment on next. First, the effect of drugs is larger for older individuals as it is shown when we compared the effect for individuals aged 65 and older versus individuals aged 45 to 64. Second, the decreasing trend on mortality rate in this period is completely explained by the change on the stock of drugs over time. To get this conclusion, we test if the year dummies are equal over time on both models and we find that the null hypothesis ($\eta_t = \eta$) cannot be rejected at 38 per cent of confidence for any of the left hand side variables considered. We can conclude that there is no additional time effect.

To check the rationality of the results in our mortality rate equation, we decompose the drug data in two sub samples. The idea is the following. Our data set contains drugs that might affect differently mortality rates. In fact, the data set includes cardiovascular-renal drugs or oncolytic drugs which are drugs attacking leading causes of death and thus we should expect a large impact of those drugs on mortality rate. The data set also includes other drugs that should not have such a big impact on mortality. This is the case of pain-relief, skin related drugs, otologic drugs or ophthalmic drugs. To test this hypothesis and check how the

model behaves in this case, we separate our sample into a first group of drugs, including these four types of drugs (pain-relief, skin, otologic, ophthalmic) and a second group including the remaining drug types. Tables 8c and 8d report the result of estimating equation (27) using these two groups.

[Insert tables 8c and 8d]

The results clearly show that the effect of the drugs over mortality rates on the first group is significatively smaller than the effect on the second group including the remainder of the drugs. For instance, the effect of drugs over mortality rates for individuals 65 years and older is only -0.02 on the first group of drugs and -0.14 on the second group.

This preliminary evidence indicates that (1) a larger number of drugs is associated with lower mortality rates and (2) this effect presents variation across drugs.

We next check these results by including additional control variables into the estimations. We report the results for the period 1980-1997 on tables 9a and 9b.

[Insert tables 9a and 9b]

In this case, we obtain similar results -when compared to tables 8a, 8b and 8c- even when we include the proxy for health expenditure and the demographic controls per therapeutic category. Further, we cannot reject the hypothesis of equal time-effects at the 54 per cent confidence for any of the cases considered. The results also show that the coefficient of health expenditure is negative, as we expected, but not significant. Thus the results are robust to the introduction of new variables to the equation.

It should be notice that neither GLS nor fixed effects address the potential simultaneity between mortality rates (and thus market size) and drugs. To address the simultaneity

problem, we propose a third estimation method. We first-differentiate equation (27) to obtain:

$$\lambda_{it} - \lambda_{it-1} = \eta_t - \eta_{t-1} + \gamma_1(SD_{it} - SD_{it-1}) + \gamma_2(h_{it} - h_{it-1}) + \gamma(Z_{it} - Z_{it-1}) + (\epsilon_{it} - \epsilon_{it-1}) \quad (28)$$

This equation is quite useful to address simultaneity because one of its right hand side variables is the flow of drugs, e.g. $FD_{it} = SD_{it} - SD_{it-1}$. This is the variable that might present simultaneity. To correct the potential bias, we instrument FD_{it} by using expected market size. The rationality of using this variable is that (1) we know it is correlated with the flow of drugs and (2) expected market size should be correlated with changes on mortality only through the creation of new drugs. Thus it is a variable that might be used as instrument for the flow of drugs in equation (28).

Table 9c presents the results of this third estimation method.

[Insert table 9c]

We obtain again a negative and significant effect of the stock of drugs. The coefficient of the stock of drugs remains similar to the values obtained above. Also the coefficient of the proxy for health expenditure has similar values to the obtained above but now the coefficient is significant.

7.5 The effect of an exogenous increase of the market size

The results show the fundamental role of population on the creation of drugs. An exogenous increase in market size produces a larger creation of drugs which affects mortality rate and thus the growth rate of population, increasing market size. This is a virtuous circle in the

creation of drugs.

To get a feeling of these effects, we will simulate an exogenous increase in drug market size where market size is defined by purchasing power of different age groups. Purchasing power is defined as population times income, and it varies across age groups ranging from 474 billion dollars in 1997 in the group of individuals aged 65 and older to 1134 billion dollars in 1997 in the group of individuals aged 35 to 44. Drug market size is defined as weighted average of these purchasing powers, and its value in 1997 is 583 billion dollars[7].

Purchasing power of elderly individuals (65 and older) is highly influenced by transfer from the government. Thus programs such as medicare and social security might considerable affect the purchasing power of these individuals. As a policy experiment, we will consider an increase on social security and medicare outlays. Suppose the government increases these outlays by approximately 36 billion dollars -which is almost a 6.5 per cent of total outlays on those items in 1998[8]. We will also assume that the policy is finance through redistribution of government outlays and thus it does not require additional taxation.

This policy has a direct impact over drug market size because it increases the purchasing power of individuals 65 and older. As these individuals represent almost a 65 per cent of drug market size[9], the implementation of the policy increases drug market size to 607 billion dollars. Thus market size rises in 4 per cent due to the government action.

We will use the information obtained above on the effects of market size over the introduction of drugs and on the effect of drugs over the mortality rate. The exogenous increase in market size is initially associated with approximately 0.08 more drugs introduced to the

[7]This value is calculated as an average across therapeutic categories

[8]source: U.S. statistical abstract, 2001

[9]This 65 per cent is the average weight across therapeutic categories of drugs of individuals 65 and older in 1997.

market -using the result obtained on tables 6 and 7. However, these new drugs reduce the mortality rates of individuals 65 and older at 0.8 per cent and thus increase market size at 0.8 per cent, producing an additional increase of drugs equal to 0.096[10]. Table 10 presents the dynamic effects of the initial 4 per cent increase on drug market size.

[Insert table 10]

The cycle continues until converging to a total increase of drugs equal to 0.1 and a total increase of market size equal to 5 per cent. Thus table shows that the initial effects of the increase of market size is stretched out. In the long run, the effects on market size and new drugs are increased by 25 per cent with respect to their initial -static- effects.

8 Conclusion

The paper shows that population is a fundamental element when analyzing the creation of new drugs. We argue that pharmaceutical firms invent new drugs based on economic incentives. A larger population, holding per capita income constant, provides a larger market size and thus incentives to invent new drugs. These drugs then affect the growth rate of population through their direct effect over the mortality rate. This feedback effect produces an additional increase in market size. These effects reinforce and produce a virtuous circle on the creation of new drugs and improvements in life expectancy.

We have provided empirical estimates that support these ideas. The estimates are quite stable under different estimation methods and they allow us to conclude that an exogenous

[10]We use the mortality rate of individuals 65 and older because individuals in this group consume more intensively drugs

shock to market size, and its corresponding initial effect in the introduction of new drugs, are amplified in 25 per cent.

Medicare and social security expenditures have interesting features in our framework. These expenditures, that affect the market size of drugs, may have an important dynamic element as they may positively affect the size of the future population receiving the same benefits, through the creation of new drugs. This is an important effect that must be considered by the policy makers.

9 Mathematical appendix

9.1 The second order condition

Notice that the first order condition of the household's problem can be written as:

$$-\lambda_h M_t^{(\frac{1-\varepsilon}{\varepsilon})} u_1 e^{-\rho t} e^{\int_0^t n_s - \lambda(M_s^{(\frac{1-\varepsilon}{\varepsilon})} h_s) ds} = \mu_t N_t P$$

Thus the associated second order condition is:

$$-\lambda_{hh} M_t^{2(\frac{1-\varepsilon}{\varepsilon})} u_1 e^{-\rho t} < 0 \Longrightarrow (\frac{\lambda_{hh} M_t^{(\frac{1-\varepsilon}{\varepsilon})} h_t}{\lambda_h}) < 0$$

This condition is satisfied when $\lambda_{hh} > 0$.

9.2 The utility function and the transversality condition

First, we will show that the utility function is bounded when $\rho > n$. The utility function is:

$$U = \int_0^{\infty} u_1 e^{-\rho t} e^{\int_0^t n_s - \lambda(\widetilde{h_s})\, ds}\, dt$$

Since $u_1 > 0$, the integral converges to infinity unless $\rho - n + \lambda(\widetilde{h}) > 0$. This last condition is trivially satisfied when $\rho > n$ because $n > n - \lambda(\widetilde{h})$. Thus, when $\rho > n$ the utility function is bounded.

Second, we will show that the transversality condition is satisfied when $B - \delta > \rho$. Let's define $H_t = \sum_{i=0}^{M_t} H_{it} = N_t \sum_{i=0}^{M_t} h_{it} = N_t h_t$, Where H_t is aggregated drug consumption in the household. The evolution of this variable follows:

$$H_t = H_0 e^{\int_0^t \frac{\dot{H_s}}{H_s} ds} \tag{29}$$

Where $\frac{\dot{H_s}}{H_s}$ is the growth rate of H at time s and H_0 is the consumption of drugs at t=0. Using the budget constraint and the equation (29), we get:

$$\dot{K_t} = (B - \delta)K_t - PH_t = (B - \delta)K_t - PH_0 e^{\int_0^t \frac{\dot{H_s}}{H_s} ds} \tag{30}$$

Solving this differential equation yields:

$$K_t = C_0 e^{(B-\delta)t} + C_1 e^{\int_0^t \frac{\dot{H_s}}{H_s} ds} \tag{31}$$

Where C_0, C_1 are constants of integration to be determined. Also it follows from (13) that: $\mu_t = \mu_0 e^{-(B-\delta)t}$, where $\mu_0 > 0$ is the shadow price at t=0. Using those conditions, we may write the transversality condition as in:

$$\begin{aligned}\lim_{t\to\infty} K_t\mu_t &= \lim_{t\to\infty}[C_0 e^{(B-\delta)t}\mu_0 e^{-(B-\delta)t} + C_1 e^{\int_0^t \frac{\dot{H}_s}{H_s}ds}\mu_0 e^{-(B-\delta)t}] \\ &= \lim_{t\to\infty}[\mu_0 C_0 + \mu_0 C_1 e^{\int_0^t \frac{\dot{H}_s}{H_s}ds-(B-\delta)t}] = 0 \end{aligned} \tag{32}$$

To satisfy the transversality condition, we require $C_0 = 0$ and $\lim_{t\to\infty} e^{\int_0^t \frac{\dot{H}_s}{H_s}ds-(B-\delta)t} = 0$. This second condition holds if $\frac{\dot{H}}{H} - (B-\delta) < 0 \Rightarrow \frac{\dot{K}}{K} - (B-\delta) < 0 \Rightarrow P\frac{H}{K} > 0$. We may replace the growth rate of H with the growth rate of H because in the long run K and H must grow at the same rate [11].

Solving for $P\frac{H}{K}$, plus the assumption $\rho > n$, yield:

$$P\frac{H}{K} > \rho[\frac{(\varepsilon-1)(1+\sigma_\lambda)}{\varepsilon-(1+\sigma_\lambda)}] + (r_t-\rho)[\frac{-(1+\sigma_\lambda)}{\varepsilon-(1+\sigma_\lambda)}] \tag{33}$$

Hence $P\frac{H}{K} > 0$ when the right hand side of (33) is positive. A sufficient condition is $r_t = B-\delta > \rho$. Thus it follows that assumption 2 assures that the utility function is bounded and the transversality condition holds.

[11] Since $C_0 = 0$, we have:

$$K_t = (\frac{C_1}{H_0})H_0 e^{\int_0^t \frac{\dot{H}_s}{H_s}ds} = (\frac{C_1}{H_0})H_t \Rightarrow \frac{H}{K} = \frac{C_1}{H_0} \Rightarrow \frac{\dot{H}}{H} = \frac{\dot{K}}{K}$$

10 Figures and tables

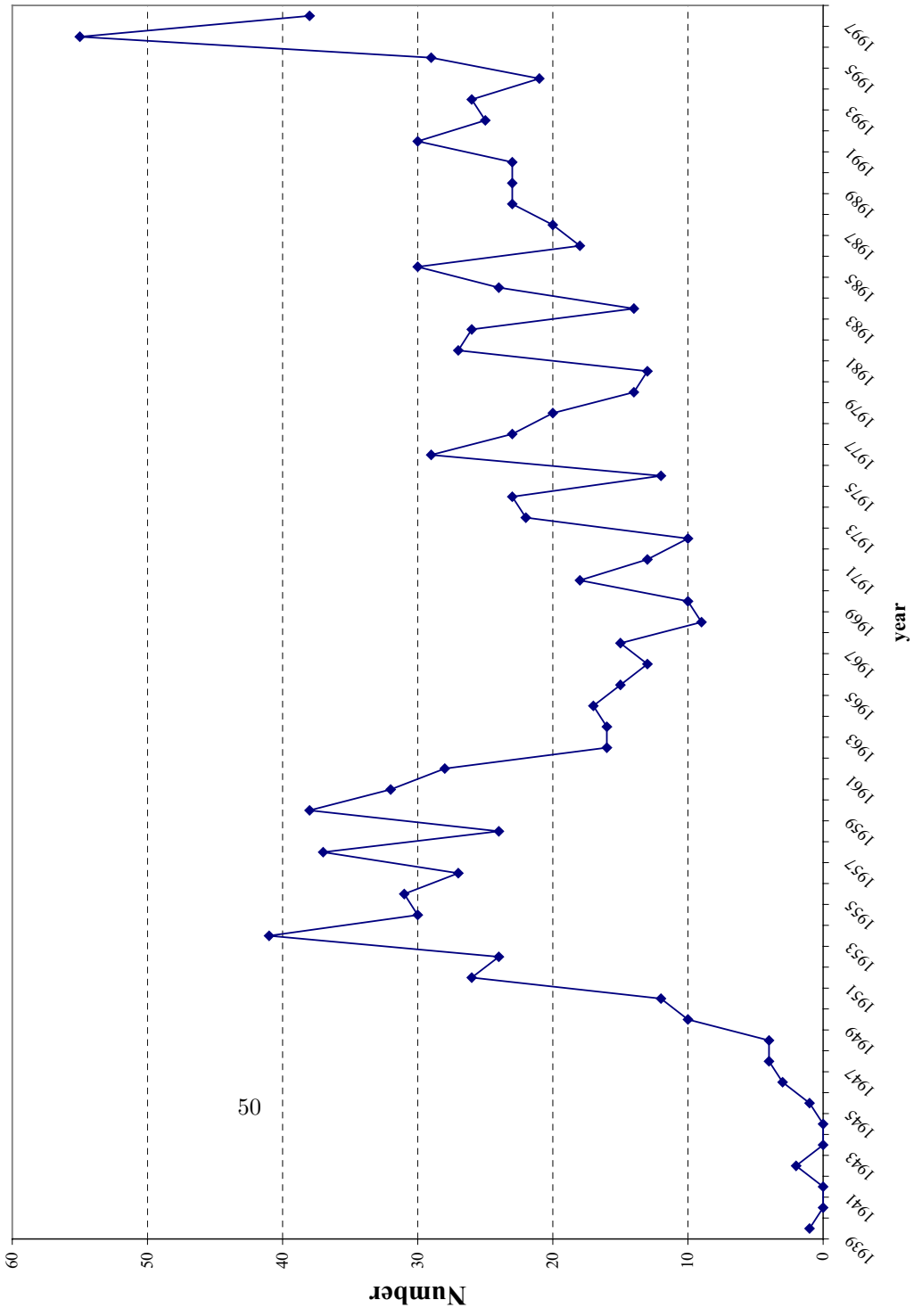

Figure 1: New Molecules Approved by FDA

Figure 2: Evolution of Mortality rate and Stock of Drugs

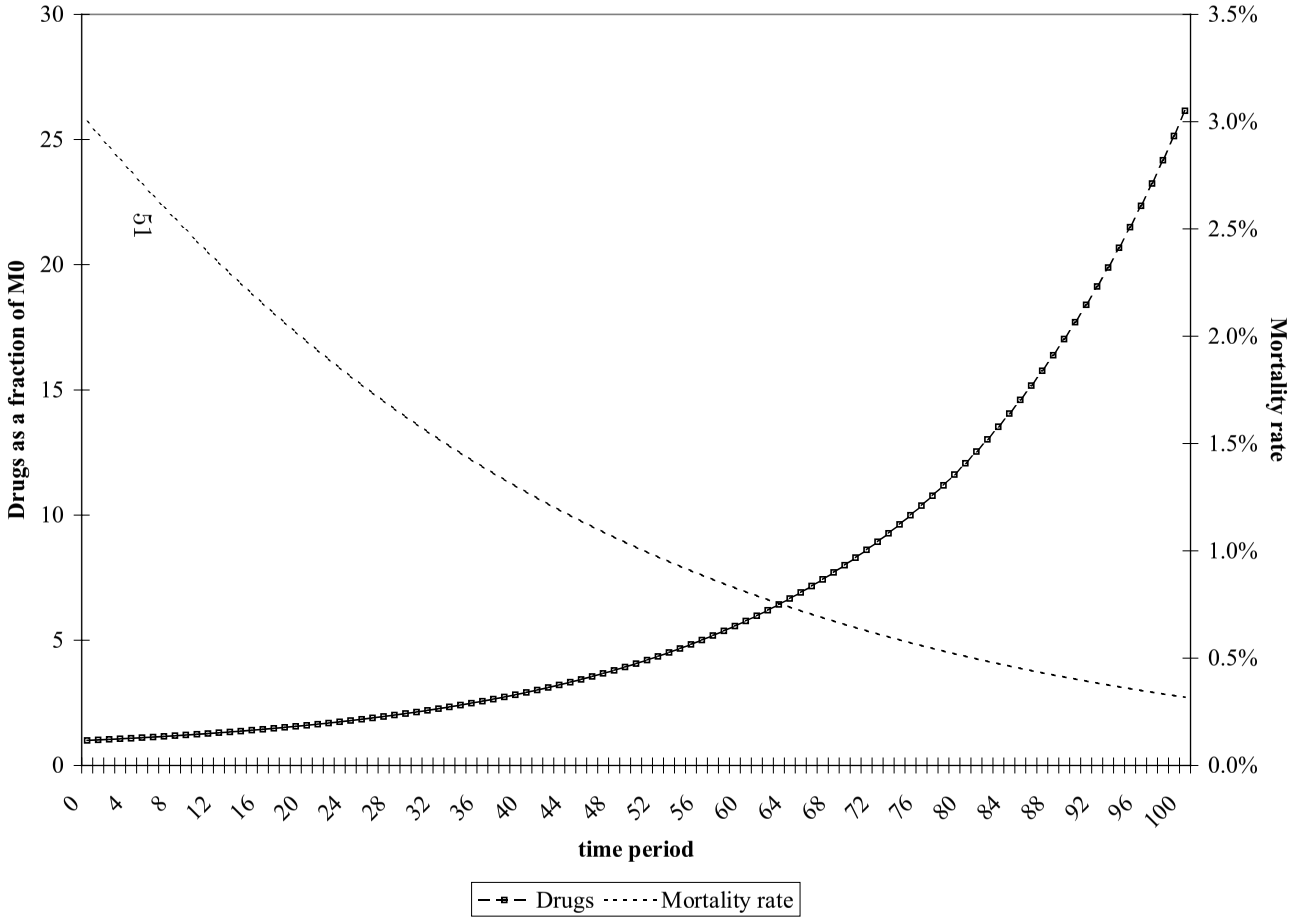

Figure 3: New drugs vs growth rate of population 65 years and older

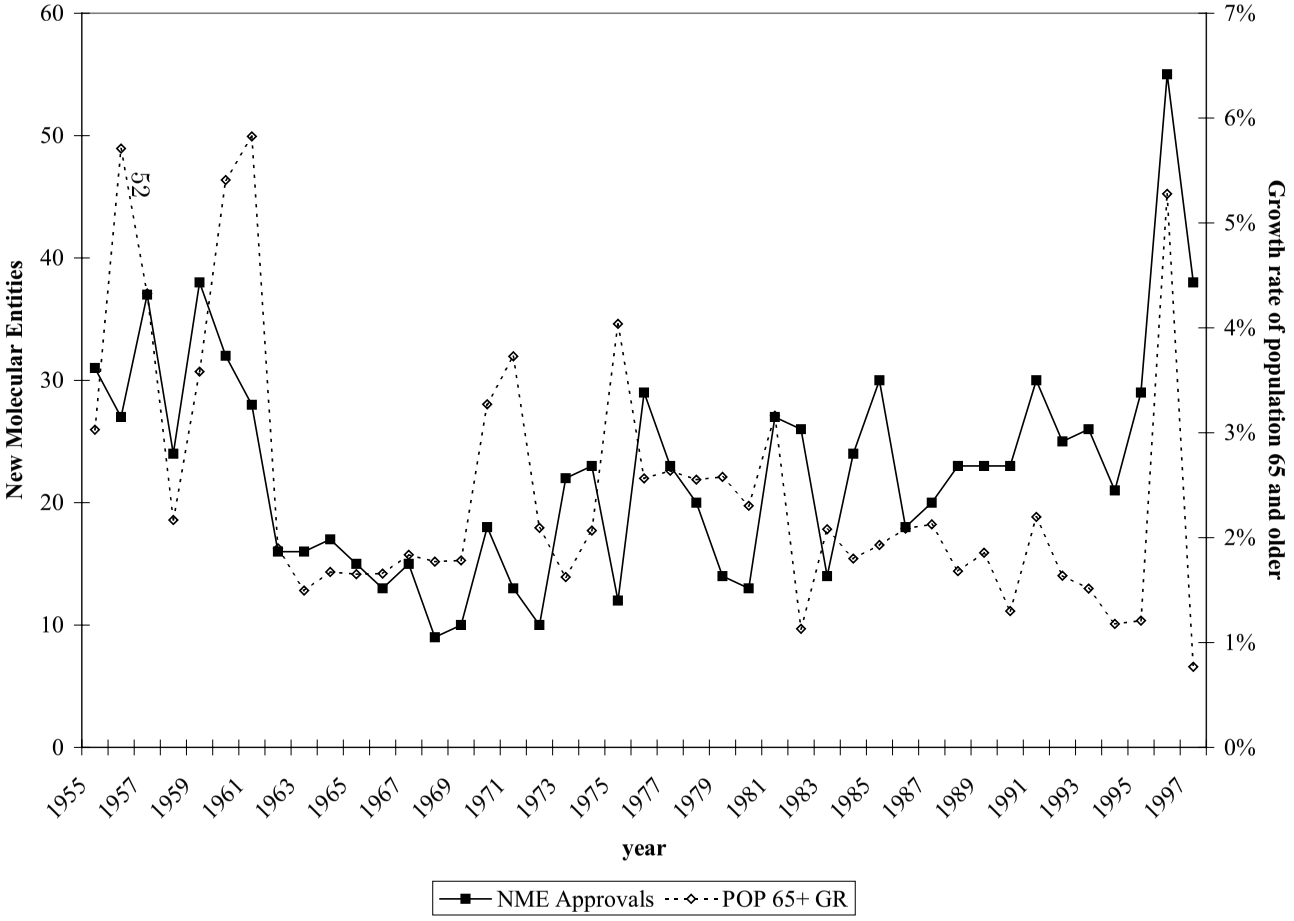

Figure 4: New drugs vs growth rate of population aged 45 to 64 years old

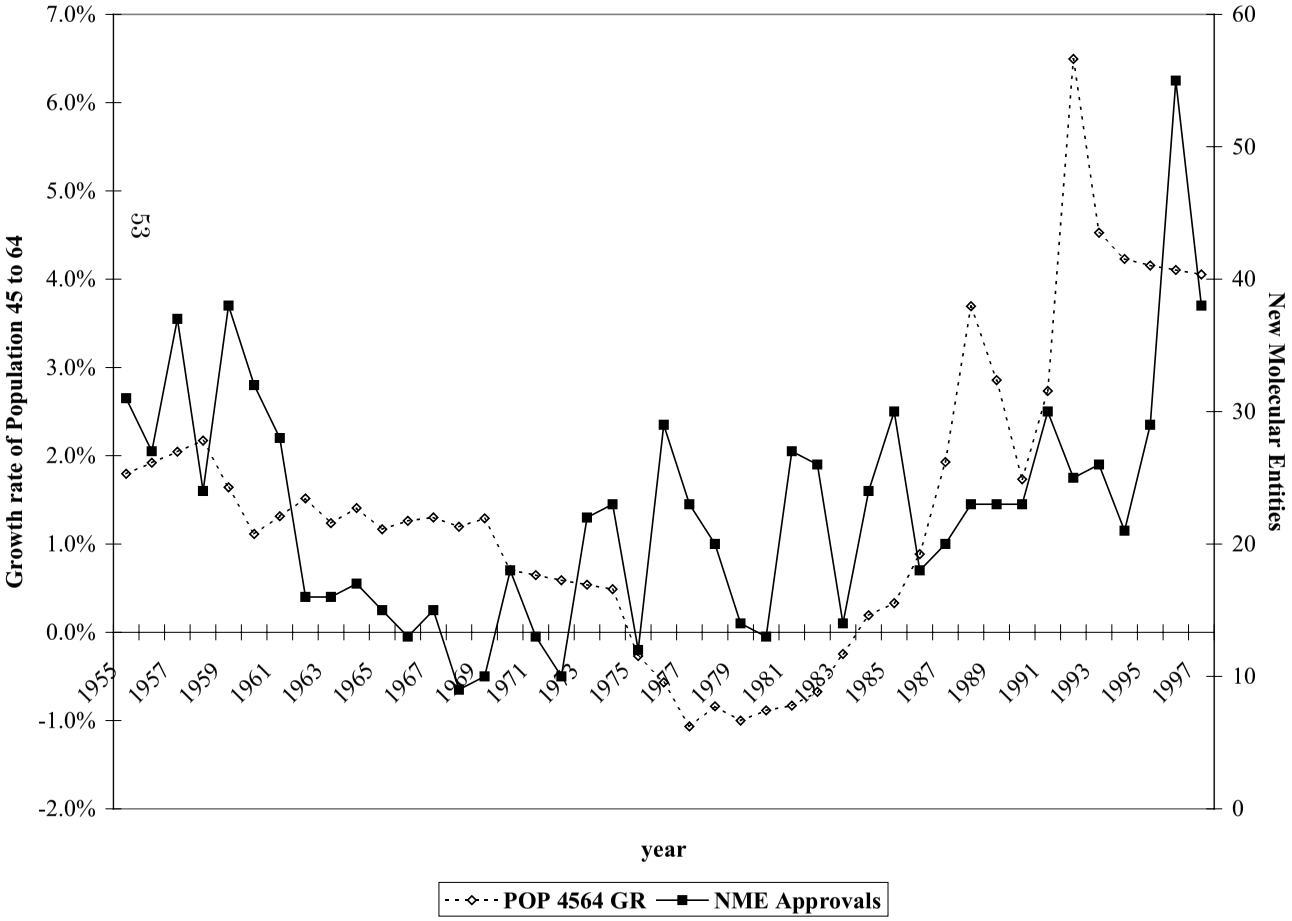

Table 1

National Drug Code Directory versus International Classification of Diseases (ICD-9)

DRUG CLASS	ICD-9 Classification
Antidotes	Poisoning (960-989)
Hematologic	Diseases of Blood (280-289)
Cardiovasular Renal	Diseases of the circulatory system (390-459)
Central nervous System	Diseases of the nervous system (320-359)
Gastrointestinal	Diseases of the digestive system (520-579)
Skin/Mucose Membrane	Diseases of the skin and subcutaneous tissue (680-709)
Neurologic	Mental disorders (290-319)
Oncolytics	Neoplasm (140-239)
Opththalmics	Diseases of the eye and ADNEXA (360-379)
Otologics	Diseases of the ear and mastoid process (380-389)
Relief of Pain	Injury (800-959)
Respiratory tract	Diseases of the respiratory track (460-519)
Antiparasitics/ Antimicrobial/ Inmunologics	Intestinal Infectious diseases (1-9), tuberculosis (10-18), Other bacterial diseases (30-41), HIV infections (042), Poliomyelitis and other…(45-49), viral diseases accompanied by exanthem (50-57), arthropod-borne viral diseases (60-66), other diseases due to viruses and chlamydiae (70-79), rickettsioses and other venereal diseases (90-99), other spirochetal diseases (100-104), mycoses (110-118), Zoonotic bacterial diseases (20-27), helminthiases (120-129), other infectious and parasitic diseases (130-136), , late effects of infectious and parasitic diseases (137-139)
Metabolic Nutrients	Nutritional deficiencies (260-269) + Other metabolic disorders (270-279)
Hormones Hormonal Mechanism	Disorders of thyroid gland (240-246) +Diseases of other endocrine glands (250-259)

Figure 5: Drugs vs Market Size

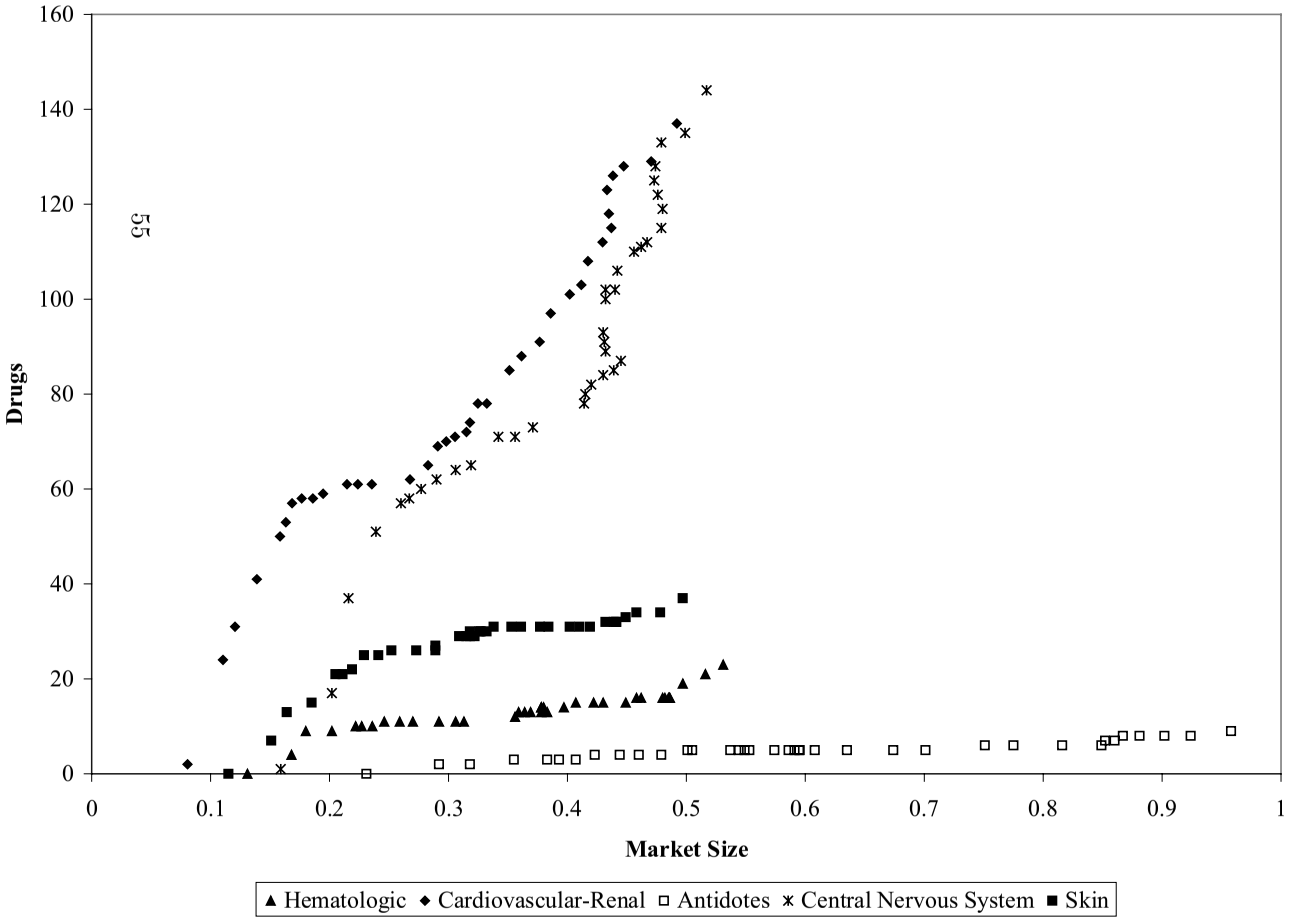

Figure 6: Drugs vs Market Size

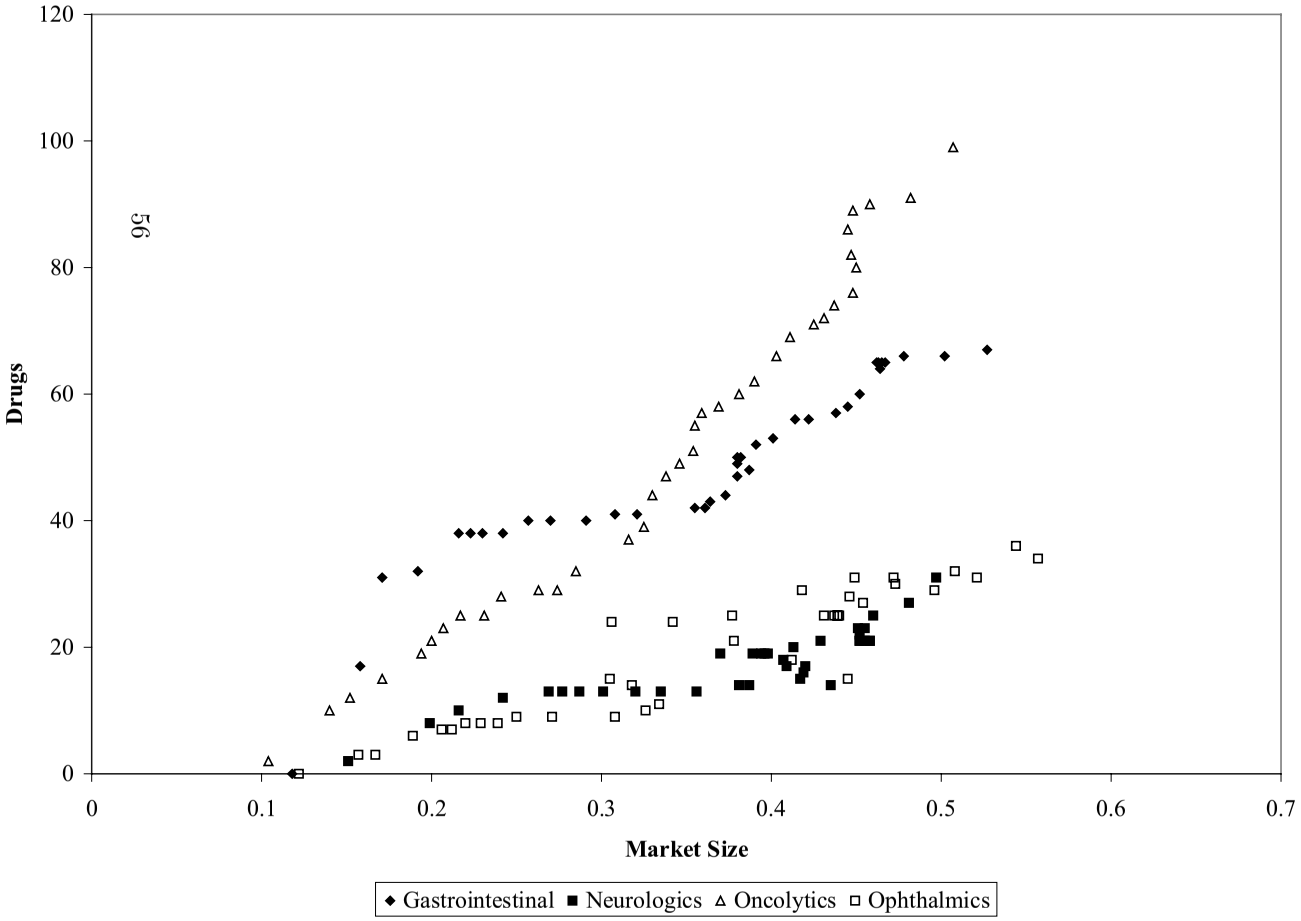

Figure 7: Drugs vs Market Size

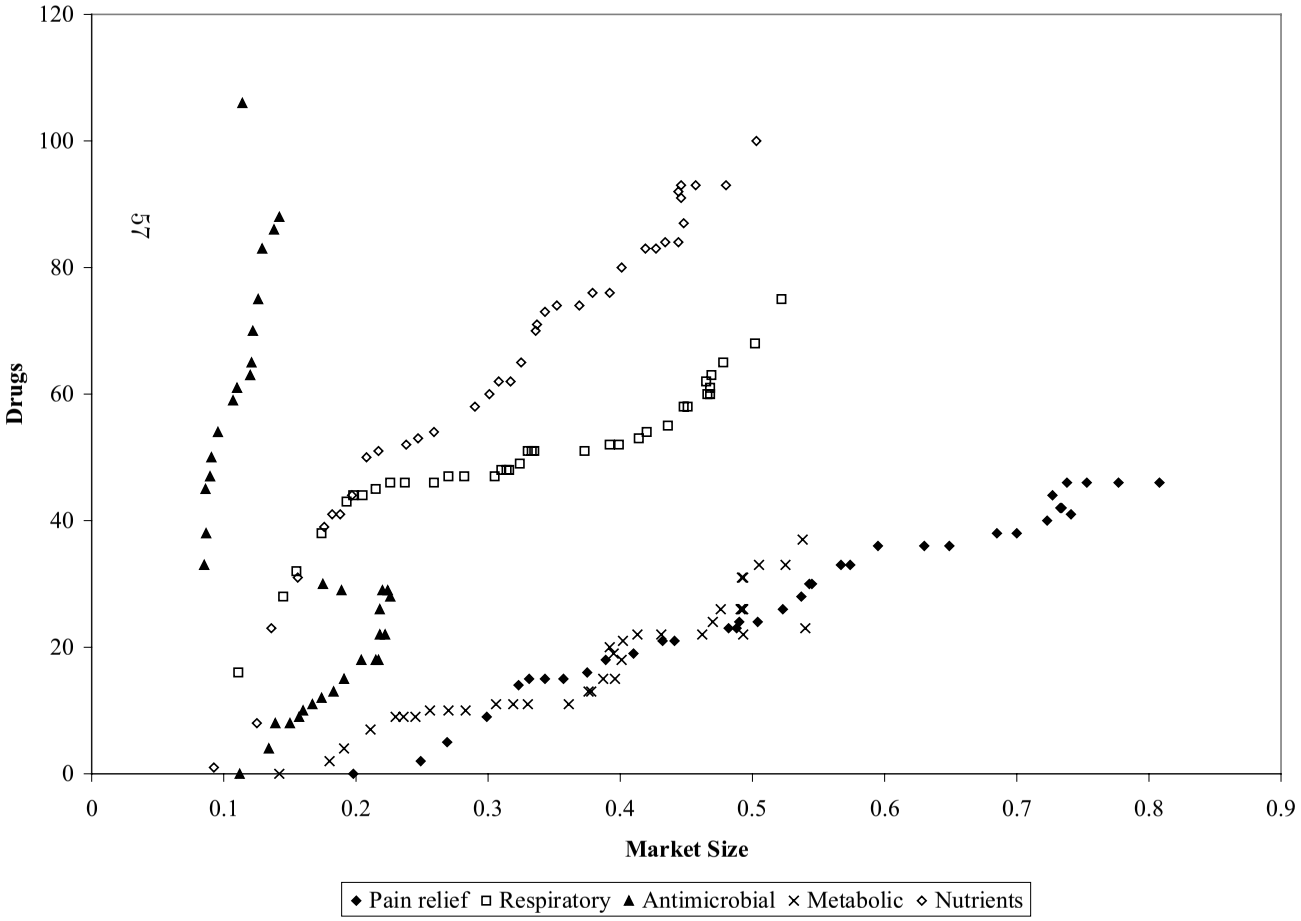

Table 2

The National Drug Code Directory And Government Grants
For Drug Related Reasearch By Institute

DRUG CLASS	Institute
Antidotes	National Center for Research Resources (NCRR) and National Institutes of General Medical Sciences (NIGMS)
Hematologic	National Heart, Lung and Blood Institute (NHLBI)
Cardiovasular Renal	National Heart, Lung and Blood Institute (NHLBI)
Central nervous System	National Institute of Mental Health (NIMH)
Gastrointestinal	National Institute of Diabetes, Digestive and Kidney Disease (NIDDK)
Skin/Mucose Membrane	National Institute of Arthritis, Musculosketal And Skin Diseases (NIAMS)
Neurologic	National Institute of Neurologic Disorders And Stroke (NINDS)
Oncolytics	National Cancer Institute (NCI)
Opththalmics	National Eye Institute (NEI)
Otologics	National Institute of Deafness And Other Communication Disorders (NIDCD)
Relief of Pain	National Center for Research Resources (NCRR) and National Institutes of General Medical Sciences (NIGMS)
Respiratory tract	National Heart, Lung and Blood Institute (NHLBI)
Antiparasitics/ Antimicrobial/ Inmunologics	National Institute of Allergies and Infectuous Diseases (NIAID)
Metabolic Nutrients	National Center for Research Resources (NCRR) and National Institutes of General Medical Sciences (NIGMS)
Hormones Hormonal Mechanism	National Center for Research Resources (NCRR) and National Institutes of General Medical Sciences (NIGMS)

Table 3: Summary statistics

	Variable	Mean	Std. Dev.	Max.	Min.
Flow of Drugs					
	Antidotes	0.15	0.36	1	0
	Hematologic	0.44	0.79	3	0
	Cardiovascular Renal	2.39	2.05	7	0
	Central nervous system	2.53	2.53	12	0
	Gastrointestinal	1.15	1.69	7	0
	Skin / Mucosa membrane	0.64	1.11	5	0
	Neurologic	0.54	0.82	4	0
	Oncolytics	1.73	1.45	5	0
	Opththalmics	0.61	0.91	3	0
	Otologics	0.02	0.13	1	0
	Pain Relief	0.81	1.01	3	0
	Respiratory track	1.29	1.47	7	0
	Antiparasitics	1.90	2.54	14	0
	Antimicrobial Immunologics				
	Metabolic	0.69	1.07	5	0
	Hormones	1.75	1.80	6	0
Market size	(Thousand billion dollars)				
	Antidotes	0.60	0.20	0.96	0.23
	Hematologic	0.36	0.11	0.53	0.13
	Cardiovascular Renal	0.30	0.12	0.49	0.08
	Central nervous system	0.39	0.09	0.52	0.16
	Gastrointestinal	0.36	0.11	0.53	0.12
	Skin / Mucosa membrane	0.33	0.10	0.50	0.12
	Neurologic	0.38	0.09	0.50	0.15
	Oncolytics	0.33	0.11	0.51	0.10
	Opththalmics	0.36	0.12	0.56	0.12
	Otologics	0.44	0.13	0.66	0.17
	Pain Relief	0.53	0.17	0.81	0.20
	Respiratory track	0.34	0.12	0.52	0.11
	Antiparasitics	0.15	0.05	0.23	0.09
	Antimicrobial Immunologics				
	Metabolic	0.38	0.11	0.54	0.14
	Hormones	0.32	0.11	0.50	0.09
Population	(Thousands)				
	25 to 34	33372	8410	43236	22153
	35 to 44	28895	6992	43998	21450
	45 to 54	23584	3145	33633	17342
	55 to 64	19554	2541	22220	13294
	65 and older	24273	6223	34076	12270
Gov. Res. Grants	(Thousands dollars)				
	NCRR	446883	139268	781358	291902
	NIGMS	699072	147578	966967	498130
	NHLBI	626720	337380	1100980	45515
	NIMH	288877	192521	685150	4995
	NIDDK	460050	189828	676399	21605
	NIAMS	194596	21522	229904	147280
	NINDS	359426	157115	599770	20011
	NCI	612450	336104	1100490	73457
	NEI	194529	63504	277721	91588
	NIDCD	148194	17342	167557	111008
	NIAID	357892	237436	896510	12333

Figure 8: Flow of drugs vs Market size

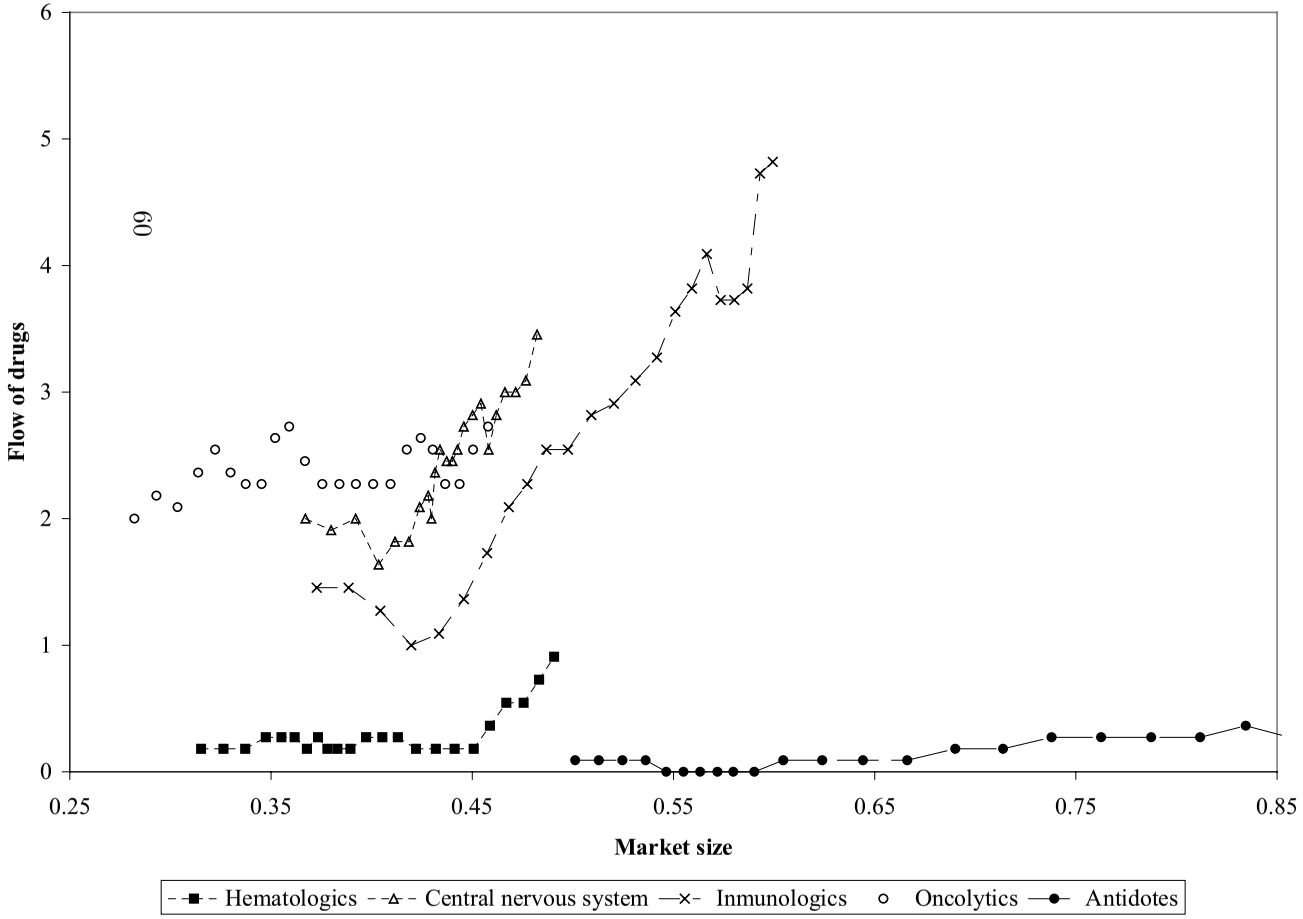

Figure 9: Flow of Drugs vs Market Size

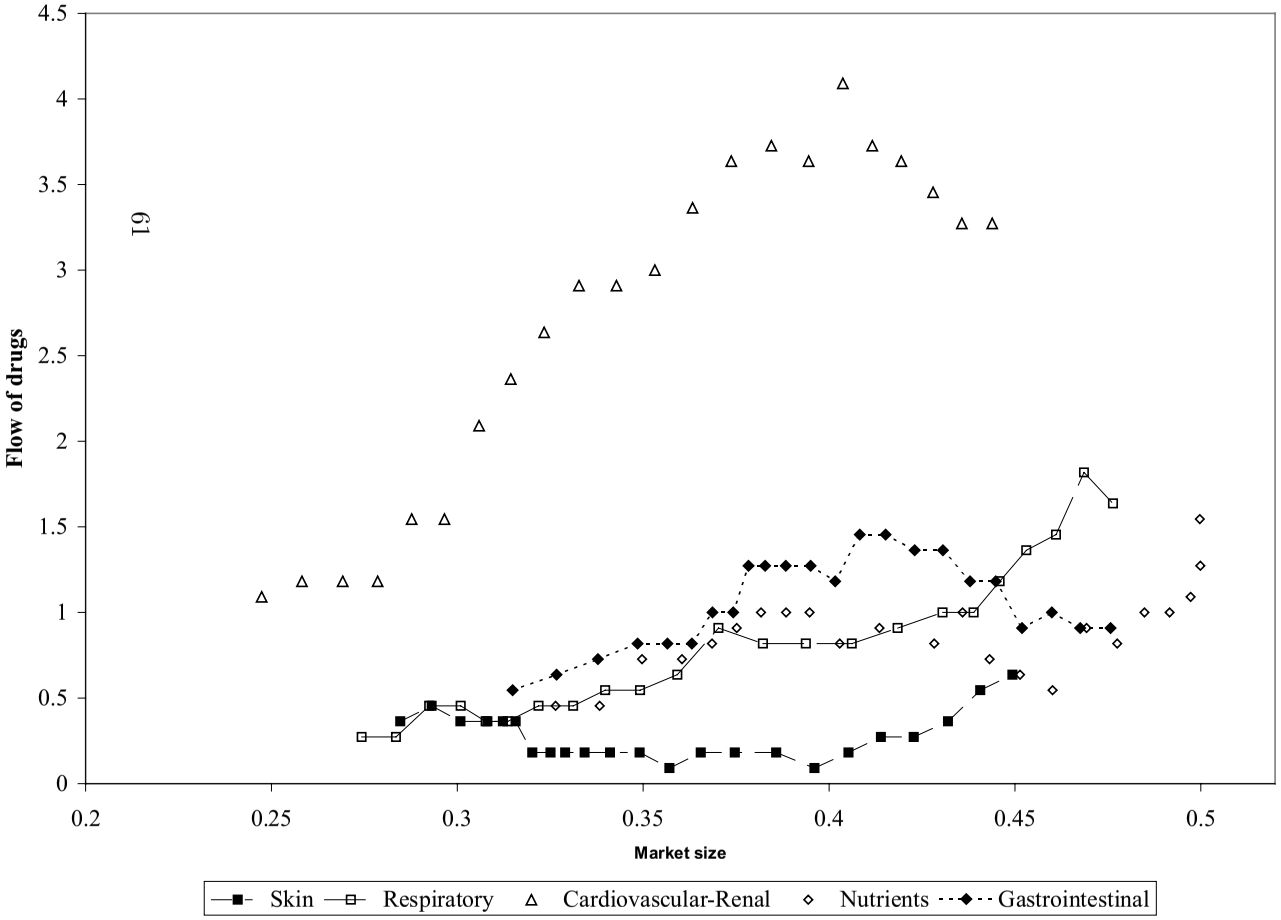

Figure 10: Flow of drugs vs Market size

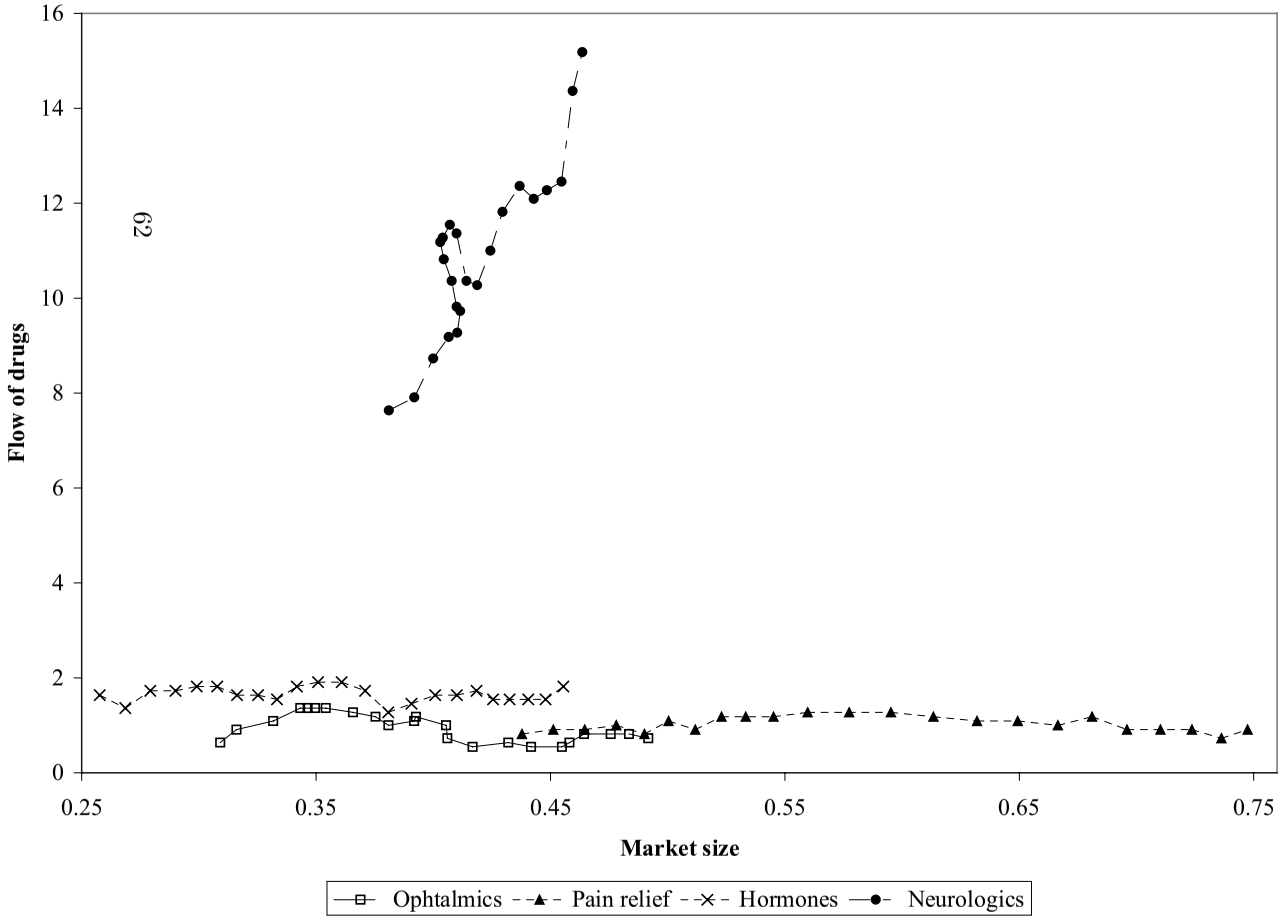

Table 4: Market size and drug creation by decades

	Variable	1960-69	1970-79	1980-89	1990-97
Antidotes	Flow of drugs	0.2	0	0.2	0.25
	Market size	0.42	0.55	0.70	0.9
Hematologics	Flow of drugs	0.2	0.3	0.2	1.25
	Market size	0.25	0.36	0.43	0.50
Cardiovascular Renal	Flow of drugs	2	1.7	3.7	3.25
	Market size	0.18	0.28	0.38	0.45
Central Nervous System	Flow of drugs	2.2	1.8	2.8	3.75
	Market size	0.29	0.42	0.45	0.49
Gastrointestinal	Flow of drugs	0.9	0.9	1.5	0.38
	Market size	0.24	0.36	0.42	0.48
Skin	Flow of drugs	1.2	0.3	0.2	0.75
	Market size	0.23	0.31	0.38	0.46
Neurologics	Flow of drugs	0.2	0.5	0.2	1.38
	Market size	0.30	0.41	0.42	0.47
Oncolytics	Flow of drugs	1.7	2.5	2.3	2.8
	Market size	0.22	0.33	0.41	0.47
Opththalmics	Flow of drugs	0.4	1.4	0.6	0.8
	Market size	0.23	0.35	0.43	0.51
Otologics	Flow of drugs	0	0.1	0	0.1
	Market size	0.3	0.42	0.53	0.61
Pain relief	Flow of drugs	1.2	0.9	1.2	0.8
	Market size	0.36	0.50	0.64	0.76
Respiratoty	Flow of drugs	0.9	0.4	0.9	2.0
	Market size	0.22	0.31	0.41	0.48
Immunologics	Flow of drugs	1.0	1.2	3.5	5.9
	Market size	0.29	0.44	0.55	0.60
Metabolic	Flow of drugs	0.4	0.9	0.6	1.9
	Market size	0.26	0.37	0.46	0.51
Nutrients	Flow of drugs	2.3	1.9	1.4	2.0
	Market size	0.20	0.30	0.40	0.46

Market size is measured in terms of 1997 billions of dollars. To construct market size we use current income for different age categories.

Table 5: Summary statistics of mortality rates 1968-1997

Mortality rates	mean	std.	max	min
antidotes	0.094	0.018	0.059	0.125
hematologic	0.029	0.006	0.012	0.038
cardiovascular-renal	3.32	1.19	2.23	5.21
central nervous system	0.11	0.042	0.039	0.200
gastrointestinal	0.31	0.036	0.178	0.369
skin- mucosae membrane	0.012	0.002	0.004	0.016
neurologic	0.066	0.034	0.207	0.154
oncolytic	1.78	0.203	0.838	1.933
ophthalmic	0.0001	0.00004	0.00003	0.0001
otologic	0.0005	0.0003	0.0001	0.001
pain relief	0.51	0.106	0.336	0.688
immunologic	0.29	0.209	0.097	0.619
metabolic	0.045	0.016	0.014	0.073
hormones	0.18	0.031	0.097	0.242

Mortality rates are measured as death per thousands of individuals

Table 6: Market size as function of expected market size 1950-1997

variable	ln(market size)	ln(market size)
ln(exp. market size)	0.81**	0.71**
	(0.027)	(0.026)
Year dummies	yes	yes
method	GLS	FE
R-sq	0.94	0.93
N	720	720

Standard errors in parenthesis. "*" and "**" indicate the variable is significant at 0.05 and 0.01 respectively.

Table 7a: Effect of market size over flow of new drugs 1950-1997

$$FD_{it} = \alpha_i + \gamma_t + \alpha_1 MKS^*_{it} + \alpha_2 SD_{it} + \alpha_3 Gov_{it} + \alpha_4 DLEG_{it} + u_{it}$$

$$MKS^*_{it} = \sum_j \varpi^i_{jt} Pop_{jt} y_{jt}$$

variable	new drugs	new drugs	new drugs	new drugs	new drugs	new drugs
method	GLS	FE	Tobit	GLS-IV	FE-IV	Tobit-IV
stock of drugs at t-1	0.09**	0.027*	0.044**	0.10**	0.031**	0.065**
	(0.009)	(0.012)	(0.017)	(0.008)	(0.010)	(0.015)
ln(market size)	0.32	1.91**	2.94**	1.02**	1.91**	2.21**
	(0.26)	(0.51)	(0.57)	(0.42)	(0.56)	(0.73)
flow of gov. exp	9.27e-7**	1.76e-6**	3.04e-6**	8.74e-7**	1.68e-6**	2.69e-6**
	(3.80e-7)	(6.37e-7)	(5.72e-7)	(3.73e-7)	(6.48e-7)	(5.72e-7)
Legislation	-0.72	-1.93**	-5.42**	-2.53**	-1.91**	-4.71**
	(0.45)	(0.51)	(0.87)	(0.64)	(0.52)	(1.03)
Year dummies	yes	yes	yes	yes	yes	yes
Market size instrumented	no	no	no	yes	yes	yes
R-sq	0.32	0.12		0.33	0.21	
Observations	705	705	705	705	705	
Uncensored			407			407
Censored at zero			298			298

Standard errors in parenthesis. * and ** indicate the variable is significant at 0.05 and 0.01 respectively. The variable stock of drugs is measured at the end of last period. The variable "flow of gov. exp." correspond to the flow of government expenditure in research per therapeutic category. Legislation is an indicator function equal to 1 after 1962 and 0 otherwise. The variables are on levels with the exception of market size, which is measured in natural logs.

Instrument⇒ Expected market which is computed as:

$$EMK_{it} = \sum_j \varpi^i_{jt} Pop^*_{jt} y_{jt}$$

Where $\text{Pop}^*_{jt}=\text{Pop}_{j(t-10)} * (1-d^*)$, and d^* is the expected mortality rate in a 10-years horizon.

Table 7b: Effect of market size over flow of new drugs - Using permanent income

$$FD_{it} = \alpha_i + \gamma_t + \alpha_1 \widetilde{MKS}^*_{it} + \alpha_2 SD_{it} + \alpha_3 Gov_{it} + \alpha_4 DLEG_{it} + u_{it}$$

$$\widetilde{MKS}^*_{it} = \sum_j \varpi^i_{jt} Pop_{jt} y^p_{jt}$$

variable	new drugs	new drugs	new drugs	new drugs	new drugs	new drugs
method	GLS	FE	Tobit	GLS-IV	FE-IV	Tobit-IV
stock of drugs at t-1	0.104**	0.028*	0.052**	0.102**	0.032**	0.06**
	(0.007)	(0.013)	(0.016)	(0.007)	(0.013)	(0.015)
ln(market size)	0.89**	1.89**	2.64**	1.89**	1.99**	2.76**
	(0.26)	(0.37)	(0.44)	(0.36)	(0.39)	(0.56)
flow of gov. exp	8.64e-7**	1.42e-6*	2.87e-6**	7.98e-7**	1.32e-6*	2.54e-6**
	(3.60e-7)	(6.39e-7)	(5.53e-7)	(3.49e-7)	(6.44e-7)	(5.67e-7)
Legislation	-2.29**	-2.64**	-3.03**	-3.20**	-2.74**	-4.95**
	(0.50)	(0.53)	(0.69)	(0.54)	(0.54)	(0.83)
Year dummies	yes	yes	yes	yes	yes	yes
Market size instrumented	no	no	no	yes	yes	yes
R-sq	0.33	0.18		0.35		0.25
Observations	705	705	705	705	705	705
Uncensored			407			407
Censored at zero			298			298

Standard errors in parenthesis. * and ** indicate the variable is significant at 0.05 and 0.01 respectively. The variable stock of drugs is measured at the end of last period. The variable "flow of gov. exp." correspond to the flow of government expenditure in research per therapeutic category. Legislation is an indicator function equal to 1 after 1962 and 0 otherwise. The variables are on levels with the exception of market size, which is measured in natural logs.

Instrument⇒ Expected market which is computed as:

$$E\widetilde{MK}_{it} = \sum_j \varpi^i_{jt} Pop^*_{jt} y^p_{jt}$$

Where Pop^*_{jt}=$\text{Pop}_{j(t-10)} * (1 - d^*)$, and d^*, y^p_{jt} are the expected mortality rate in a 10-years horizon and permanent income.

Table 8a: Effect of drugs over mortality rates (1968-1997)

Fixed effects method

variable	Mortality rate	Mortality rate	Mortality rate
	Overall	45 to 64 years old	65 years and older
Number of Drugs	-0.014**	-0.023**	-0.13**
	(0.0018)	(2.2e-3)	(0.014)
Year dummies	yes	yes	yes
R-sq	0.18	0.14	0.18
Observations	450	450	450

Standard errors in parenthesis. * and ** indicate the variable is significant at 0.05 and 0.01 respectively. Mortality rate is measured as death per thousands of individuals while the stock of drugs is measured on levels. Both variables are measured across the 15 therapeutic categories.

Table 8b: Effect of drugs over mortality rates (1968-1997)

GLS method

variable	Mortality rate	Mortality rate	Mortality rate
	Overall	45 to 64 years old	65 years and older
Number of Drugs	-0.012**	-0.02**	-0.11**
	(0.0018)	(0.002)	(0.014)
Year dummies	yes	yes	yes
R-sq	0.18	0.13	0.17
Observations	450	450	450

Standard errors in parenthesis. * and ** indicate the variable is significant at 0.05 and 0.01 respectively. Mortality rate is measured as death per thousands of individuals while the stock of drugs is measured on levels. Both variables are measured across the 15 therapeutic categories.

Table 8c: Effect of drugs over mortality rates using two sub samples (1968-1997)

FE method-Group I

variable	Mortality rate Overall	Mortality rate 45 to 64 years old	Mortality rate 65 years and older
Number of Drugs	-0.016**	-0.025**	-0.14**
	(0.002)	(0.003)	(0.019)
Year dummies	yes	yes	yes
R-sq	0.15	0.10	0.14
Observations	330	330	330

Table 8d: Effect of drugs over mortality rates using two sub samples (1968-1997)

FE method-Group II

variable	Mortality rate Overall	Mortality rate 45 to 64 years old	Mortality rate 65 years and older
Number of Drugs	-0.0058**	-0.007**	-0.02**
	(0.001)	(0.001)	(0.003)
Year dummies	yes	yes	yes
R-sq	0.16	0.14	0.13
Observations	120	120	120

Note to tables 8c and 8d. Standard errors in parenthesis. * and ** indicate the variable is significant at 0.05 and 0.01 respectively. Mortality rate is measured as death per thousands of individuals while the stock of drugs is measured on levels. The drugs included in table 8c are: antidotes, hematologic, cardiovascular-renal, central nervous system, gastrointestinal, neurologic, oncolytic, respiratory track, immunologic, metabolic and hormones. The drugs included in table 8d are: skin-mucosae membrane, ophthalmic and otologic drugs.

Table 9a : Effect of drugs over mortality rates - Fixed effect method - Additional covariates (1980-1997)

variable	Mortality rate Overall	Mortality rate 45 to 64 years old	Mortality rate 65 years and older
Number of Drugs	-0.011**	-0.019**	-0.102**
	(0.002)	(0.0023)	(0.016)
ln(exp. on hospital beds)	-0.019	-0.020	-0.26
	(0.042)	(0.049)	(0.33)
demographics	yes	yes	yes
Year dummies	yes	yes	yes
R-sq	0.35	0.24	0.34
Observations	285	285	285

Standard errors in parenthesis. * and ** indicate the variable is significant at 0.05 and 0.01 respectively. Mortality rate is measured as death per thousands of individuals while the stock of drugs is measured on levels. The variable "exp. on hospital beds" is total expenditure per year on hospital beds. Demographics includes the fraction of males, black, white and married individuals affected by the disease. Also average age of those individuals is included.

Table 9b : Effect of drugs over mortality rates - GLS method - Additional covariates (1980-1997)

variable	Mortality rate Overall	Mortality rate 45 to 64 years old	Mortality rate 65 years and older
Number of Drugs	-0.007**	-0.013**	-0.057**
	(0.002)	(0.002)	(0.013)
ln(exp. on hospital beds)	-0.02	0.03	-0.09
	(0.042)	(0.047)	(0.031)
demographics	yes	yes	yes
Year dummies	yes	yes	yes
R-sq	0.24	0.13	0.23
Observations	285	285	285

Standard errors in parenthesis. * and ** indicate the variable is significant at 0.05 and 0.01 respectively. Mortality rate is measured as death per thousands of individuals while the stock of drugs is measured on levels. The variable "exp. on hospital beds" is total expenditure per year on hospital beds. Demographics includes the fraction of males, black, white and married individuals affected by the disease. Also average age of those individuals is included.

Table 9c : Effect of drugs over mortality rates - Additional covariates (1980-1997)

First difference of the data - Using instrument for drugs

variable	Mortality rate Overall	Mortality rate 45 to 64 years old	Mortality rate 65 years and older
Number of Drugs	-0.014**	-0.009	-0.094**
	(0.005)	(0.011)	(0.030)
ln(exp. on hospital beds)	-0.016**	-0.009	-0.12**
	(0.007)	(0.015)	(0.040)
demographics	yes	yes	yes
Year dummies	yes	yes	yes
R-sq	0.18	0.05	0.20
Observations	240	240	240

Standard errors in parenthesis. * and ** indicate the variable is significant at 0.05 and 0.01 respectively. The variables are in first differences and we instrument the first difference of the drug stock (flow of drugs) by using expected market size. Mortality rate is measured as death per thousands of individuals while the stock of drugs is measured on levels. The variable "exp. on hospital beds" is total expenditure per year on hospital beds. Demographics includes the fraction of males, black, white and married individuals affected by the disease. Also average age of those individuals is included.

Table 10: The dynamics on the creation of drugs

Initial shock of 4 per cent increase on market size

time period	Stock of drugs	accumulated change on market size
0	0	0.04
1	0.08	0.048
2	0.096	0.0496
3	0.0992	0.0499
..	..	..
12	0.1	0.125

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