The Antibiotic Era: Historical and Ethical Reflections on Seven Decades of Reform Efforts

Scott Podolsky, M.D.
Professor of Global Health and Social Medicine, Harvard Medical School
Director, Center for the History of Medicine, Countway Medical Library

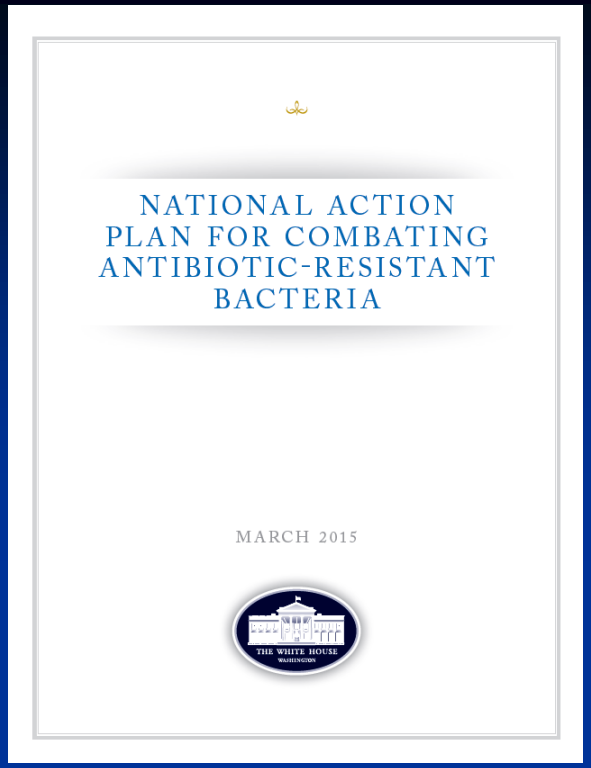
"**What is the future of antibiotics? Antibiotics are here to stay.** Others, less toxic and more active … will be found. Costs will be reduced. Side effects will be either eliminated or controlled. Physicians will have well equipped laboratories at their disposal to evaluate each antibiotic and determine at once the particular antibiotic required for the treatment of a specific disease. Self medication will be reduced to a minimum. Government control of antibiotics will be tightened, so as to render antibiotics safer, more useful, and less expensive. **The antibiotic era will accomplish what nature has intended it to be: Man's control over infectious diseases and epidemics that have plagued mankind since prehistoric times."**

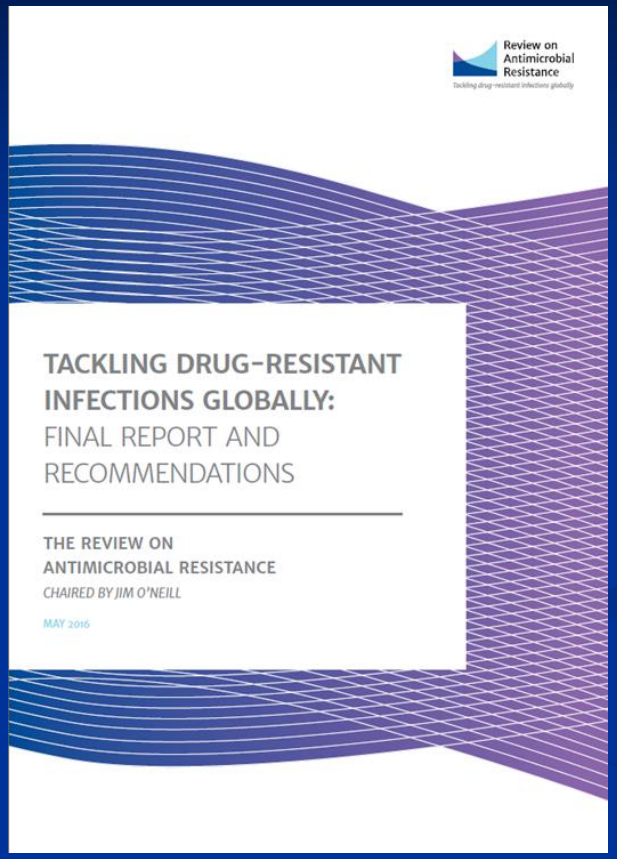
Selman A. Waksman, 1963

From the Selman Waksman papers, Rutgers University Libraries

"Antimicrobial resistance is a ticking time bomb not only for the UK but also for the world. We need to work with everyone to ensure the apocalyptic scenario of widespread antimicrobial resistance does not become a reality. This is a threat arguably as important as climate change for the world."

Dame Sally Davies,
Chief Medical Officer for England,
(first published online in 2013)


NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA
MARCH 2015
THE WHITE HOUSE
WASHINGTON


Review on Antimicrobial Resistance
Tackling drug-resistant infections globally
TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY:
FINAL REPORT AND RECOMMENDATIONS
THE REVIEW ON ANTIMICROBIAL RESISTANCE
CHAIRED BY JIM O'NEILL
MAY 2016


GLOBAL ACTION PLAN
ON ANTIMICROBIAL RESISTANCE
World Health Organization

GENERAL ASSEMBLY OF THE UNITED NATIONS

President of the 71st session

Home | General Assembly | About the President | From The President | Media | Events | SG Selection

« All Events

High-level Meeting on Antimicrobial Resistance

September 21 @ 10:00 am - 6:00 pm

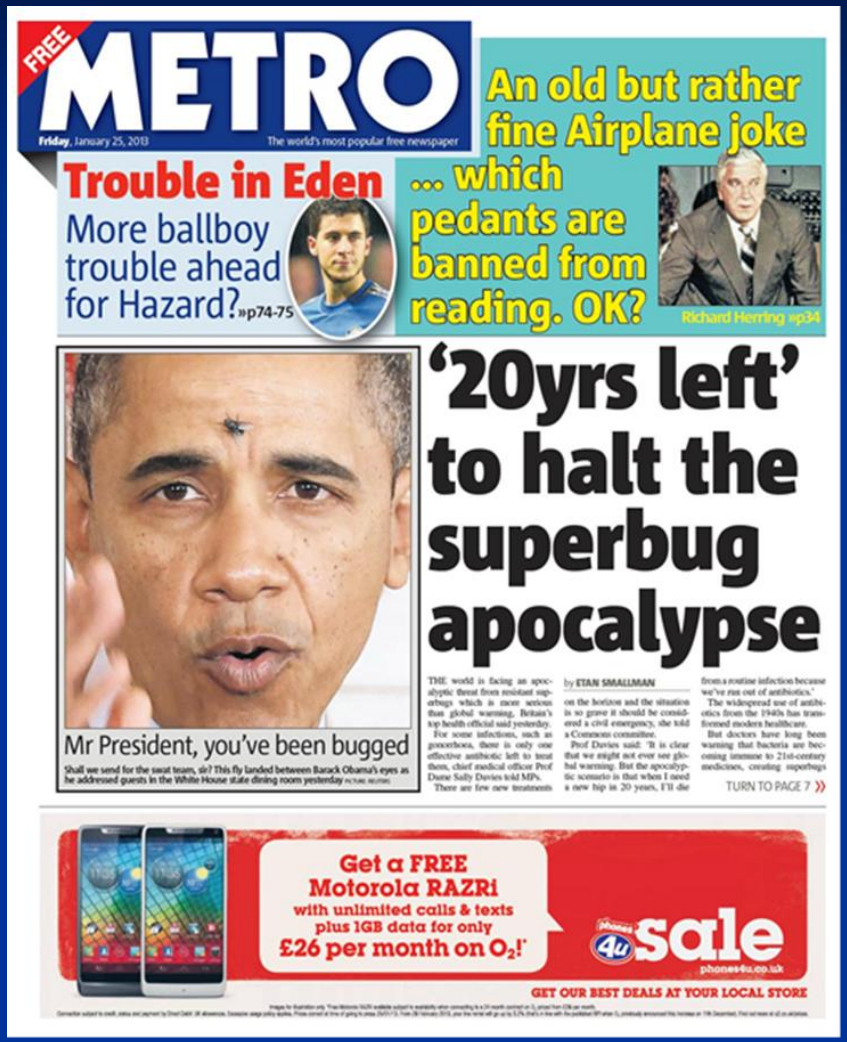
54

HIGH-LEVEL MEETING ON ANTIMICROBIAL RESISTANCE

21 SEPTEMBER 2016, UN HEADQUARTERS, NEW YORK

On 21 September 2016, the President of the UN General Assembly convenes an one-day high-level meeting at the UN Headquarters in New York on "Antimicrobial Resistance", with the participation of Member States, non-governmental organizations, civil society, the private sector and academic institutions, in order to provide input.

The primary objective of the meeting is to summon and maintain strong national, regional and international political commitment in addressing antimicrobial resistance comprehensively and multi-sectorally, and to increase and improve awareness of antimicrobial resistance.



FREE

METRO

Friday, January 25, 2013 — The world's most popular free newspaper

An old but rather fine Airplane joke ... which pedants are banned from reading. OK?

Richard Herring »p34

Trouble in Eden

More ballboy trouble ahead for Hazard? »p74-75

Mr President, you've been bugged

Shall we send for the swat team, sir? This fly landed between Barack Obama's eyes as he addressed guests in the White House state dining room yesterday PICTURE: REUTERS

'20yrs left' to halt the superbug apocalypse

by ETAN SMALLMAN

THE world is facing an apocalyptic threat from resistant superbugs which is more serious than global warming, Britain's top health official said yesterday.

For some infections, such as gonorrhoea, there is only one effective antibiotic left to treat them, chief medical officer Prof Dame Sally Davies told MPs.

There are few new treatments on the horizon and the situation is so grave it should be considered a civil emergency, she told a Commons committee.

Prof Davies said: 'It is clear that we might not ever see global warming. But the apocalyptic scenario is that when I need a new hip in 20 years, I'll die from a routine infection because we've run out of antibiotics.'

The widespread use of antibiotics from the 1940s has transformed modern healthcare.

But doctors have long been warning that bacteria are becoming immune to 21st-century medicines, creating superbugs

TURN TO PAGE 7 »

Source: IBM (online, 2013)

Are germs winning the war against people?

RECENT REPORTS in medical journals and the press warn that the problem of controlling infectious disease caused by bacteria may be getting out of hand. The first break in our defenses against bacterial infection appeared almost as soon as "wonder drugs" were developed, with the discovery of bacteria that were resistant to the new antibiotics. Now, scientists have found that many types of bacteria have acquired the ability to *pass* this resistance on to each other faster even than people spread germs in epidemics.

Medical authorities regard this situation as the most serious development in the field of infectious disease over the past decade—for a reason that has not been sufficiently stressed in press reports: Bacteria can spread their resistance not just to one but to *several* antibiotics at a time. And the bitterest irony of all is that the use of antibiotics actually aggravates this situation.

Doctors can no longer afford to prescribe antibiotics as freely as too many have been doing for too long. Some scientists feel that the use of antibiotics must be sharply curtailed in medicine and in the meat- and poultry-raising industries as well. If not, they say, we may find ourselves no better off than we were in the 1930's, before the advent of sulfa drugs and penicillin, when cleanliness was about the only weapon we had against bacterial infection.

This situation has many medical authorities deeply worried. It is so new that the problem of controlling it cannot yet even be defined. This is particularly disconcerting because the germs involved can cause everything from food poisoning and typhoid fever to cholera and plague.

The problem of transmissible bacterial drug resistance was thought, as late as 1962, to be confined to the Far East. Since then, it has popped up in Germany, Israel, Britain, Holland, Switzerland, Greece and—most recently—the United States. The first news of contagious bacterial drug resistance in this country appeared in the July 2 issue of *Lancet*, a British medical journal. It came from the Harvard Medical School, where Dr. David H. Smith reported that this was the most common form of drug resistance in a wide variety of bacterial infections he had examined in Boston hospitals. Dr. Smith believes it presents a serious hazard to the public health and urges that a national survey of the problem be undertaken.

The story of how medical scientists discovered the problem goes back to the 1950's, when Japanese bacteriologists were studying the *Shigella* bacterium's resistance to antibiotics. This bacterium is a principal cause of dysentery.

Classically, bacteria become resistant to an antibiotic by mutating, or changing, their hereditary makeup, so that the drug does not kill them. For example, one out of approximately every hundred million bacteria will mutate to resist the effects of streptomycin, even in the absence of the drug. In the presence of the drug, however, the resistant bacterium has a survival advantage over its vulnerable neighbors, which succumb. The mutant bacterium then has a clear field in which to multiply and build up a population of cells that are completely resistant to streptomycin.

Japanese scientists discovered in 1955 that some *Shigellae* bacteria were resistant not just to one but to three or four very different drugs: sulfonamides, streptomycin, tetracycline and chloramphenicol. The mutation theory did not apply. It would account for the development of resistance to *one* drug at a time, not three or four at once.

In addition, Japanese doctors discovered that some dysentery patients carried both *Shigellae* bacteria that were resistant to three antibiotics, and another very different bacterium that was resistant to the same three drugs.

Those two observations made it appear that resistance to several antibiotics at once was actually being passed from one bacterium to another in "packages" of three or four resistance traits.

Not only are germs developing resistance to "wonder drugs," but they're passing on this resistance to each other

Japanese bacteriologists proved this theory in 1959. Scientists later learned that the packages of multiple drug resistance could, themselves, multiply in bacteria, and that they were passed from cell to cell on contact. The resistance traits apparently achieve their protective effects by preventing certain antibiotics from getting into the bacterial cell.

Scientists do not yet know where drug-resistance traits come from. They do know that they exist in many kinds of bacteria. They also know that bacteria that are sensitive to drugs can "catch" from other bacteria resistance to *all the most effective antibiotics used in medicine today.*

Dr. E. S. Anderson of Britain's Public Health Service has even found a Superbug that carries resistance to more than seven powerful antibacterial agents: streptomycin, tetracycline, chloramphenicol, sulfonamides, neomycin, kanamycin and the penicillins.

What causes bacteriologists great concern is the prospect that such a bug might get loose and create an epidemic of invulnerability to drugs among germs throughout the world. This could conceivably happen if the spread of these multiple-resistant germs is not checked.

Studies in Japan and Britain have shown unequivocally that the use of antibiotics encourages the spread of multiple-drug resistance factors in bacteria. For example, suppose that a few of Dr. Anderson's Superbugs were lurking in a mass of bacteria sensitive to tetracycline. Administration of that antibiotic would kill the sensitive germs all right, but a host of Superbugs would be spawned as a consequence.

Sparing use of antibiotics would lessen the spread of bacterial drug resistance. Also, because the resistance traits are unstable, and frequently disappear spontaneously, not bringing them out with antibiotics may eventually make them vanish.

There is no doubt among authorities that the rise in the number of multiply-resistant bacteria is due largely to the imprudent use of antibiotics in medicine and their widespread use—for treating and preventing infection—in the raising of cattle and poultry. This latter application has greatly improved the quantity and quality of meat in this country; it is uncertain what effect curtailing the use of antibiotics would have on meat production.

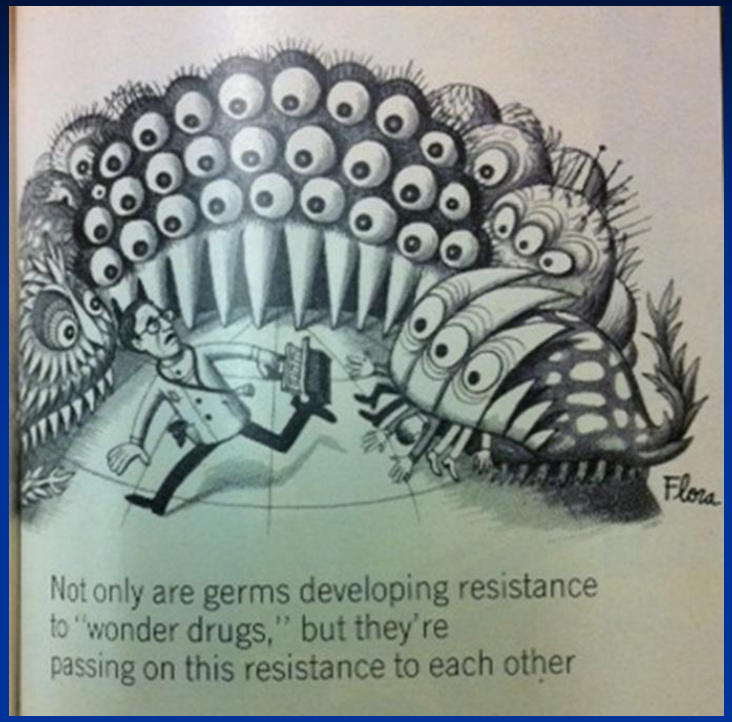
Nevertheless, Dr. Anderson, who has studied bacterial drug resistance in cattle fed on antibiotic-treated feed, has declared that "The time has clearly come for a reexamination of the whole question of the use of antibiotics and other drugs in the rearing of livestock."

And Dr. Naomi Datta of the Postgraduate Medical School of London, where she has studied the problem in humans, insists that "antibiotics should be reserved for when really necessary."

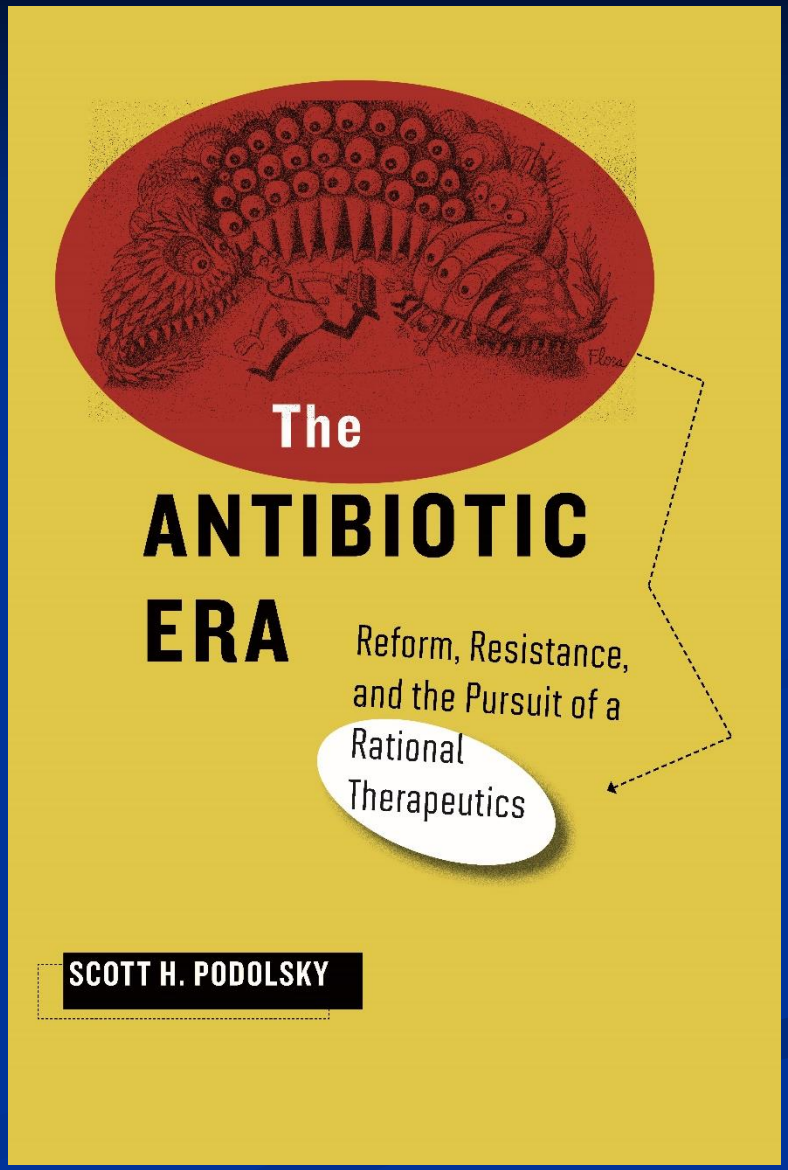
Meanwhile, the pharmaceutical industry is working harder than ever to develop *new* antibiotics so that we can at least stay even in the war against our bacterial enemies.

JOHN A. OSMUNDSEN

DRAWING BY JAMES FLORA



Look magazine, 10/18/66, first use of the term "superbug" to refer to resistant microbes



Outline

I. The Broad Spectrum Revolution(s)

II. Antibiotics, the FDA, and the Controlled Clinical Trial

III. Confronting the "Superbug"

IV. Conclusion: The Pursuit of a Rational Therapeutics

Antibiotics and ethics, historically speaking …

Has **seldom** been about: Negative externalities of antibiotic use or the tragedy of the commons, though the tension between present and future patients has been an enduring concern.

Has **often** been about:

a) The role of the investigator and the clinician against the influence of the marketplace; in other words, a "rational therapeutics" as a linked moral, methodological, and pragmatic undertaking, manifesting, e.g., as concerns about conflict of interest, the role and proper conduct of the clinical trial, the role of the clinician as educator (rather than mere prescriber) to one's patients, and the ultimate delivery of the right drug to the right patient at the right time.

b) Increasing attention to the linked moral and pragmatic aspects of global infectious disease itself, and the structures determining care delivery and who gets sick in the first place.

I. The Broad-Spectrum Revolution(s)

"Doctor, why is aureomycin best?"

Have you ever wondered why doctors prescribe AUREOMYCIN for so many *different* illnesses? There are many reasons, which may be summed up by describing this versatile drug as at present the nearest approach to a "perfect" antibiotic.

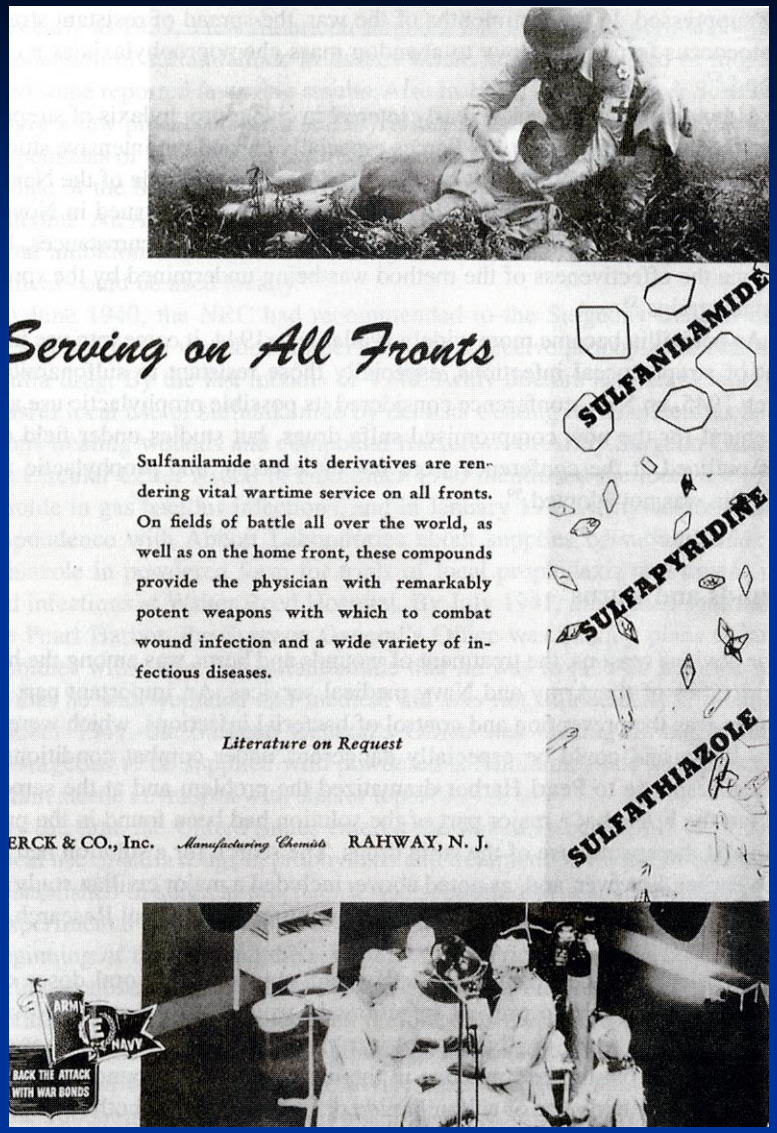
The medical literature, which already contains over 7,000 references to AUREOMYCIN, continues to give proof of its effectiveness against an increasing number of infections. In many cases, it has proved successful where other antibiotics have failed. Experience has shown that AUREOMYCIN achieves better results with lower dosages . . . without serious side reactions . . . and with less likelihood that disease germs will build up immunity to its health-restoring powers.

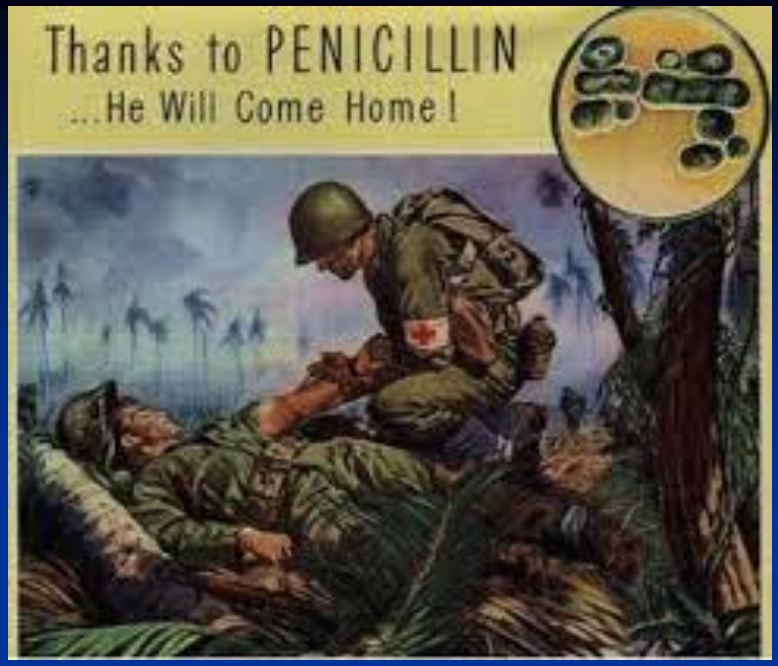
AUREOMYCIN, developed by Lederle Laboratories Division of American Cyanamid Company, is today hailed by the medical profession as the greatest of the new weapons against infectious disease.

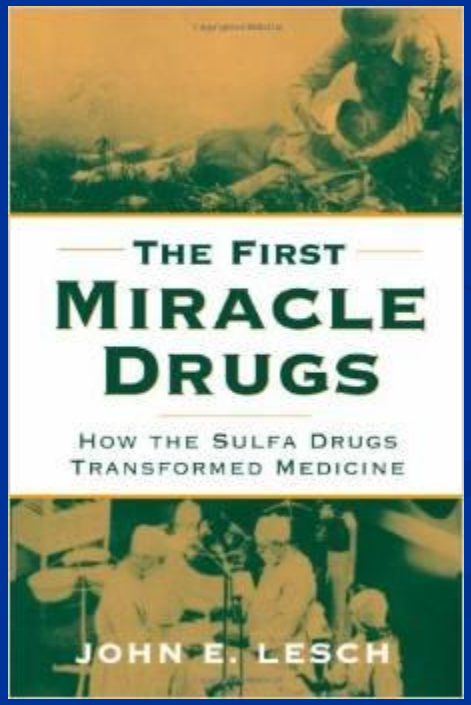
AMERICAN Cyanamid COMPANY

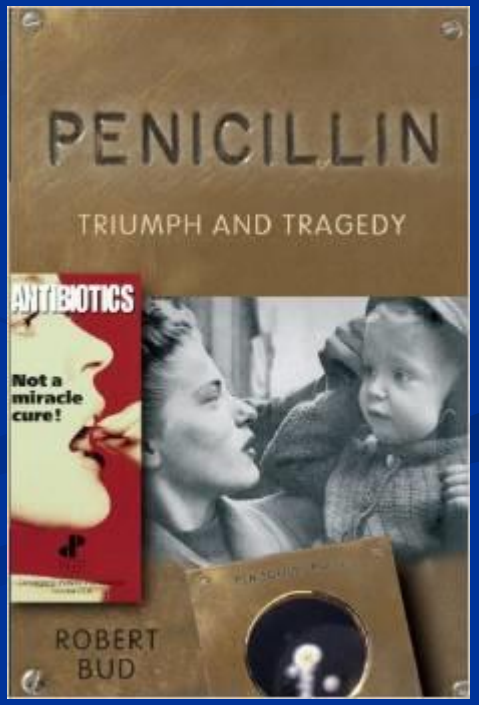
30 ROCKEFELLER PLAZA, NEW YORK 20, N. Y.

Materials for the Medical Profession—one of Cyanamid's Many Services


Serving on All Fronts
SULFANILAMIDE
SULFAPYRIDINE
SULFATHIAZOLE
Sulfanilamide and its derivatives are rendering vital wartime service on all fronts. On fields of battle all over the world, as well as on the home front, these compounds provide the physician with remarkably potent weapons with which to combat wound infection and a wide variety of infectious diseases.
Literature on Request
ERCK & CO., Inc. Manufacturing Chemists RAHWAY, N. J.
ARMY NAVY
BACK THE ATTACK WITH WAR BONDS


Thanks to PENICILLIN
...He Will Come Home!


THE FIRST
MIRACLE DRUGS
HOW THE SULFA DRUGS TRANSFORMED MEDICINE
JOHN E. LESCH


PENICILLIN
TRIUMPH AND TRAGEDY
ANTIBIOTICS
Not a miracle cure!
ROBERT BUD

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AMERICAN *Cyanamid* COMPANY
30 ROCKEFELLER PLAZA, NEW YORK 20, N. Y.

Materials for the Medical Profession—one of Cyanamid's Many Services

Chloromycetin

BROAD SPECTRUM
OF SPECIFIC ANTIBIOTIC ACTIVITY

CLINICALLY IMPORTANT INDICATIONS INCLUDE:

- UNDULANT FEVER
- BACILLURIA
- SALMONELLOSIS
- SURGICAL INFECTIONS
- TYPHOID FEVER
- TYPHUS FEVER
- SCRUB TYPHUS
- ROCKY MOUNTAIN SPOTTED FEVER
- PSITTACOSIS
- LYMPHOGRANULOMA VENEREUM
- PRIMARY ATYPICAL PNEUMONIA

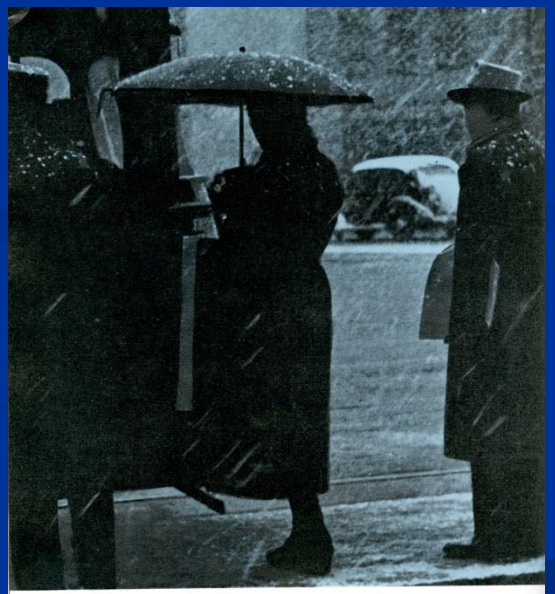
● Chloromycetin* (Chloramphenicol, Parke-Davis) is a pure crystalline substance with specific antibiotic activity effective against an impressive list of micro-organisms.

The first antibiotic for therapeutic use that can be produced in quantities by either natural fermentation or chemical synthesis, Chloromycetin is perorally potent and relatively safe in recommended dosage. Average initial peroral dosage is 60 mg. per kilogram (3 to 4 Gm. in three doses at hourly intervals) followed by 0.25 Gm. every four hours.

Chloromycetin is available in 0.25 Gm. Kapseals® (sealed gelatin capsules); bottles of 12.

*Trade-mark

PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN



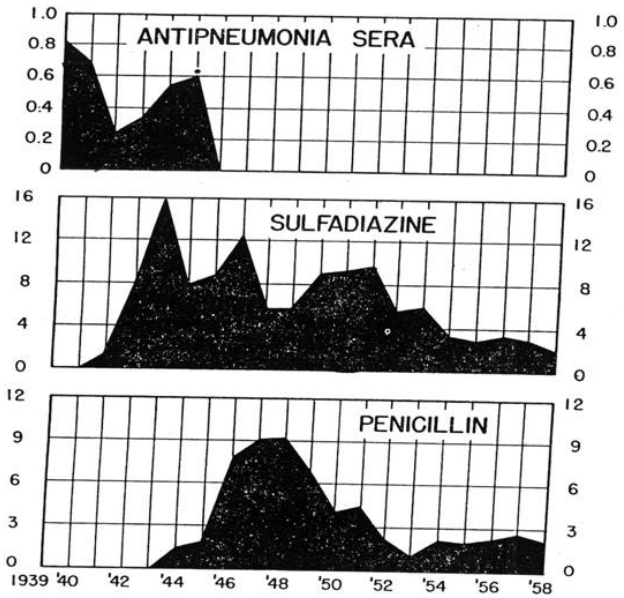
the season for respiratory tract infections—a time for Terramycin

The value of Terramycin in promptly controlling otitis media, severe sinusitis, laryngotracheobronchitis, and virtually all infections of the respiratory tract due to, or complicated by, the many organisms sensitive to Terramycin is now a matter of clinical record. The excellent toleration and the rapid response noted with the use of Terramycin particularly recommends it as a therapy of choice for respiratory tract infections. Among the convenient dosage forms of Terramycin are Capsules, Tablets (sugar coated), good-tasting, nonalcoholic Oral Suspension and Pediatric Drops and Intravenous for hospital use in severe or fulminating acute infections.

Pfizer

LEDERLE'S ANTIBACTERIAL DRUGS HAVE A HIGH RATE OF OBSOLESCENCE

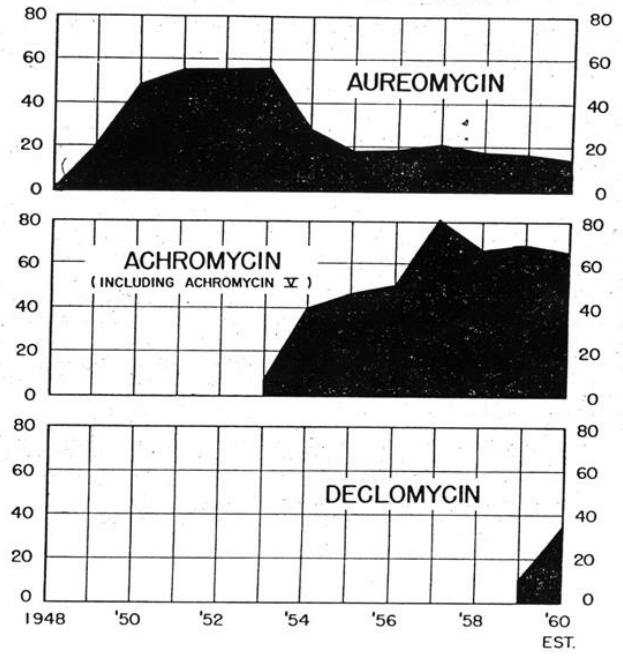
(SALES IN MILLIONS OF DOLLARS)

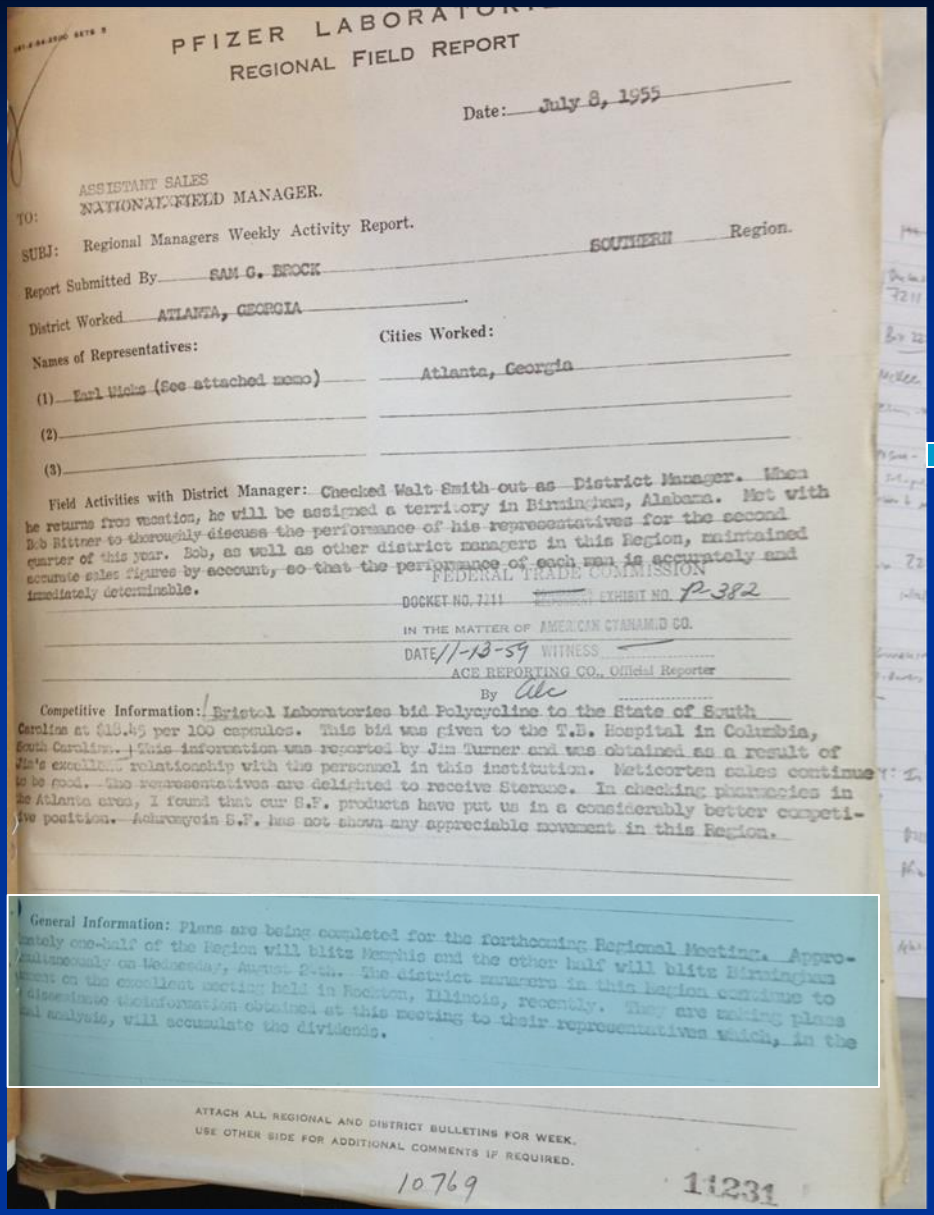


*PEAK DUE TO WARTIME GOVERNMENT PURCHASES

LEDERLE'S ANTIBACTERIAL DRUGS HAVE A HIGH RATE OF OBSOLESCENCE

(SALES IN MILLIONS OF DOLLARS)





PFIZER LABORATORIES

REGIONAL FIELD REPORT

Date: July 8, 1955

TO: ASSISTANT SALES NATIONAL FIELD MANAGER.

SUBJ: Regional Managers Weekly Activity Report.

Report Submitted By SAM G. BROCK SOUTHERN Region.

District Worked ATLANTA, GEORGIA

Names of Representatives: Cities Worked:

(1) Earl Hicks (See attached memo) Atlanta, Georgia

(2)

(3)

Field Activities with District Manager: Checked Walt Smith out as District Manager. When he returns from vacation, he will be assigned a territory in Birmingham, Alabama. Met with Bob Bittner to thoroughly discuss the performance of his representatives for the second quarter of this year. Bob, as well as other district managers in this Region, maintained accurate sales figures by account, so that the performance of each man is accurately and immediately determinable.

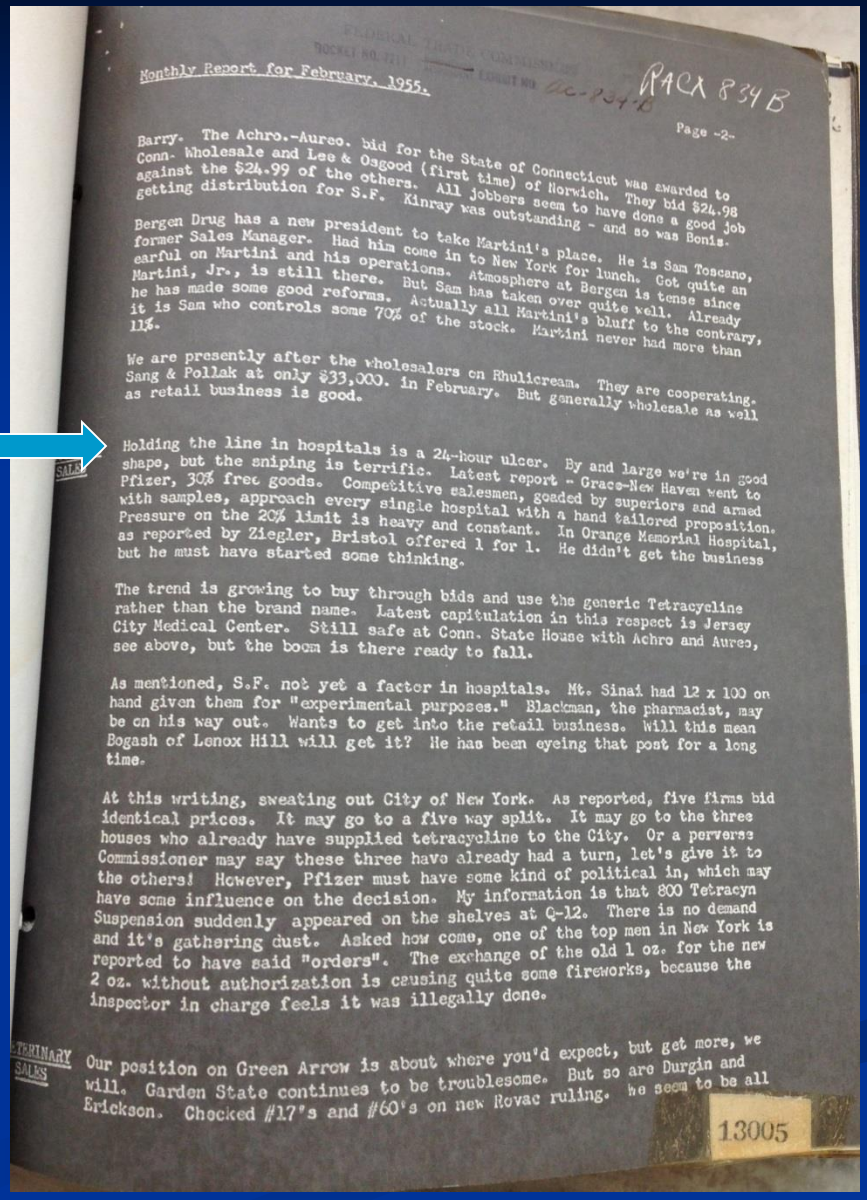
FEDERAL TRADE COMMISSION
DOCKET NO. 7211 EXHIBIT NO. P-382
IN THE MATTER OF AMERICAN CYANAMID CO.
DATE 1-13-59 WITNESS
ACE REPORTING CO., Official Reporter
By

Competitive Information: Bristol Laboratories bid Polycycline to the State of South Carolina at $18.85 per 100 capsules. This bid was given to the T.B. Hospital in Columbia, South Carolina. This information was reported by Jim Turner and was obtained as a result of Jim's excellent relationship with the personnel in this institution. Meticorten sales continue to be good. The representatives are delighted to receive Sterane. In checking pharmacies in the Atlanta area, I found that our S.F. products have put us in a considerably better competitive position. Achromycin S.F. has not shown any appreciable movement in this Region.

General Information: Plans are being completed for the forthcoming Regional Meeting. Approximately one-half of the Region will blitz Memphis and the other half will blitz Birmingham simultaneously on Wednesday, August 24th. The district managers in this Region continue to comment on the excellent meeting held in Rockton, Illinois, recently. They are making plans to disseminate the information obtained at this meeting to their representatives which, in the final analysis, will accumulate the dividends.

ATTACH ALL REGIONAL AND DISTRICT BULLETINS FOR WEEK.
USE OTHER SIDE FOR ADDITIONAL COMMENTS IF REQUIRED.

10769 11231



RACX 834B

Monthly Report for February, 1955.

Page -2-

Barry. The Achro.-Aureo. bid for the State of Connecticut was awarded to Conn. Wholesale and Lee & Osgood (first time) of Norwich. They bid $24.98 against the $24.99 of the others. All jobbers seem to have done a good job getting distribution for S.F. Kinray was outstanding - and so was Benis.

Bergen Drug has a new president to take Martini's place. He is Sam Toscano, former Sales Manager. Had him come in to New York for lunch. Got quite an earful on Martini and his operations. Atmosphere at Bergen is tense since Martini, Jr., is still there. But Sam has taken over quite well. Already he has made some good reforms. Actually all Martini's bluff to the contrary, it is Sam who controls some 70% of the stock. Martini never had more than 11%.

We are presently after the wholesalers on Rhulicream. They are cooperating. Sang & Pollak at only $33,000. in February. But generally wholesale as well as retail business is good.

SALES

Holding the line in hospitals is a 24-hour ulcer. By and large we're in good shape, but the sniping is terrific. Latest report - Grace-New Haven went to Pfizer, 30% free goods. Competitive salesmen, goaded by superiors and armed with samples, approach every single hospital with a hand tailored proposition. Pressure on the 20% limit is heavy and constant. In Orange Memorial Hospital, as reported by Ziegler, Bristol offered 1 for 1. He didn't get the business but he must have started some thinking.

The trend is growing to buy through bids and use the generic Tetracycline rather than the brand name. Latest capitulation in this respect is Jersey City Medical Center. Still safe at Conn. State House with Achro and Aureo, see above, but the boom is there ready to fall.

As mentioned, S.F. not yet a factor in hospitals. Mt. Sinai had 12 x 100 on hand given them for "experimental purposes." Blackman, the pharmacist, may be on his way out. Wants to get into the retail business. Will this mean Bogash of Lenox Hill will get it? He has been eyeing that post for a long time.

At this writing, sweating out City of New York. As reported, five firms bid identical prices. It may go to a five way split. It may go to the three houses who already have supplied tetracycline to the City. Or a perverse Commissioner may say these three have already had a turn, let's give it to the others! However, Pfizer must have some kind of political in, which may have some influence on the decision. My information is that 800 Tetracyn Suspension suddenly appeared on the shelves at Q-12. There is no demand and it's gathering dust. Asked how come, one of the top men in New York is reported to have said "orders". The exchange of the old 1 oz. for the new 2 oz. without authorization is causing quite some fireworks, because the inspector in charge feels it was illegally done.

VETERINARY SALES

Our position on Green Arrow is about where you'd expect, but get more, we will. Garden State continues to be troublesome. But so are Durgin and Erickson. Checked #17's and #60's on new Rovac ruling. He seem to be all

13005

Federal Trade Commission records, National Archives

FEDERAL TRADE COMMISSION
DOCKET NO. 7211 COMMISSION EXHIBIT NO. P-429 PX 429
RESPONDENT
IN THE MATTER OF AMERICAN CYANAMID CO.
DATE 1-12-59 WITNESS
ACE REPORTING CO., Official Reporter
By alc

October 8, 1954

TO: ALL DISTRICT MANAGERS IN THE SOUTHERN REGION

FROM: SAM G. BROCK

SUBJECT: EASY PREY FOR TERRAMYCIN.

Computations from the latest Market Research Report reveal that the leading tetracycline product has advanced 4% during July and August over May and June. During this same period, Terramycin sales dropped 1/2 percentage point. This gain of tetracycline was picked up from a loss in Aureomycin sales. In other words, Aureomycin continues to account for a sizeable portion of the over-all market.

Competition is switching Aureomycin users directly to tetracycline. This is understandable since competition is deliberately selling Aureomycin down the river.

What do we do? We will help them to reduce the sale of Aureomycin by switching these doctors directly to Terramycin. Your men have a vast knowledge and experience in the ways and means to combat Aureomycin with a good solid Terramycin detail. Let's pick up the trail of all physicians who are using Aureomycin and concentrate on switching them to our side of the fence. Your representatives should know which doctors are using Aureomycin, which is the first step in the program.

On the more encouraging side, we continue to enjoy the leading position in private hospital purchases with Terramycin; however, tetracycline is showing some in-roads into the business. The next few weeks will be a very critical period, and may form the pattern for many months to come. It is imperative that you keep abreast of every situation in your district and waste no time in lending your full support to the troubled areas.

Your men should be impressed fully with the importance of their wholehearted and best efforts. There is no reason whatsoever why Terramycin and Tetracyn should not form the leading group of wide spectrum antibiotics.

SGB:mf

cc: Mr. T. G. Bradley
Mr. George Guess
Mr. C. H. Barwick
Mr. H. R. Stewart

ttached card has been distributed to druggists for their use by Sharp & Dohme in the Wilkes Barre area.

R. W. Hodgdon, Philadelphia salesman, reports that Lilly is hiring non-pharmacists, that two have been hired in the Philadelphia area, and that Lilly now has a district manager for administration purposes and a field man who goes out with the men.

A Philadelphia physician reports that Pfizer, Upjohn and Schering are employing third and fourth year medical students to detail physicians during their summer vacations and he thinks this is a wonderful idea.

R. Greenspan, Philadelphia salesman, reports that his personal physician, a D.O., told him that Pfizer took the D.O.'s of the Philadelphia area, out to a country club and gave them a big time. Within a month a detail man arrived at the doctor's office, asked him if he had had a good time and said that Pfizer expected him to write for their products in the future. The D.O. was insulted and since then refuses to write for any Pfizer product.

Pfizer had a regional sales meeting on August 18 at the Shoreham Hotel, Washington, D.C. On Friday, previous to the meeting, a general blitz of Washington, D.C., was effected. Results will be watched carefully.

Mr. R. Miller, Baltimore District hospital salesman, reports seeing an invoice in Thomas & Thompson Drug Store, Baltimore, showing 500 mg. Tetracyn I.V., 500 vials, billed on a drop-shipment basis to the Baltimore City Hospital, at a price of $2.13 per vial, less 10% handling charge. According to Miller's information, Pfizer will ship at the same price in much smaller quantities. This is the first break seen in that area, of prices below the recently established city, county, state price.

District Manager Walker reports that trends toward Lilly's Compren have not changed noticeably. Doctors have told our salesman, A. D. Snyder, that when given a choice of capsules to take during pregnancy, the women always chose the brightly colored Lilly Compren. This may be one approach that the Lilly men is using.

GENERAL

The Uevral Ping-Pong Ball is one of the most effective detailing pieces yet given us. The salesmen seem to be enthused about it. However, one difficulty is that the ball does not jump up as it is supposed to do and District Manager Zemany suggests that if more are made, that the paper under the ball be made just a little stiffer for greater resiliency. Doctors are amused by this device and usually want more of them.

J.F.Hanifan

13021

Federal Trade Commission records, National Archives

RACX 753 B

FEDERAL TRADE COMMISSION
DOCKET NO. 7211 RESPONDENT EXHIBIT NO. ac-753-B
Page -2-

To: Mr. C. K. Piercy

Jersey City was an out and out handout. It all went to Squibb. I asked Don Brown for a full report, copy of which is attached for your information and files.

In Connecticut, this last time, the bid was split between Conn. Wholesale Drug in Waterbury, and Lee & Osgood Wholesale Drug in Norwich. They each bid $25.49, underbidding others by 1¢. We were fearful we would lose out with the long price but we gambled the district manager knew what he was doing when he insisted we could get the business. We had him call on the State Purchasing Agent twice to make sure. However, this was the last time. Local suppliers will not be supported against the going bid of $22.49.

Mr. Muenzberg checks with this region on all City, County, and State bids. Invariably, we ask him to bid the low net price.

Another word on samples. S.F. has not been significant anywhere. A program in hospitals seems to have developed whereby Pfizer leaves 3 to 6, 100's, in the pharmacy; then goes upstairs and leaves plenty in the wards; further, the head of the Formulary Committee or the superintendent, or both, are seen, told about it and promised additional supplies in two weeks. The approach sometimes get real crude. "It's your business to save the hospital money. This generous supply costs the hospital nothing." This hospital force-feeding was first reported from Long Island where their Sales Ed. chief did the job. But it has since come from all areas.

Mysteclin has appeared in some hospitals. Panmycin does not seem to be in step locally with the reports we receive.

In the doctors' offices, sampling has become a scandal. Packages of 10's are given lavishly. As a result of one detail a doctor may find himself with as much as $20. or $30. in material. A strong temptation for him to sell, - he can't possibly use it all. This gives the peddlers another inning.

Hear of blitzing now and then, but not as before. Latest, blitz by six Pfizer men in Ulster, Dutchess, Orange, and Sullivan Counties. Also, for the week of April 18th, Pfizer is sending 15 men into Long Island and Queens. They have had poor luck in this area.

Entertainment. Hospital Staffs have been provided cocktails, (in one case it turned out to be beer - which did not make the internes happy). Buffets, golf, and golf prizes also are provided. Cannot help but feel that our tours and symposia are what Pfizer is trying to offset. One very annoying result of all this cocktail pampering is that we are getting an ever-increasing number of such requests ourselves. More try it, and more ask for more and more.

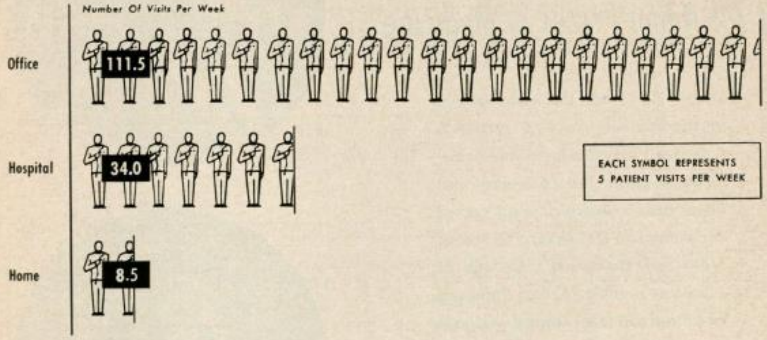
I'm afraid this is overlong but it is difficult to reduce all to writing. Mention of one thing evokes another. However, you have, with this, a fair picture of what is going on in this area. It's fast getting out of hand. The level of business conduct has fallen to that of the cheapest chiseler. Always, there has to be a gimmick. As much is being given away as is sold.

11936

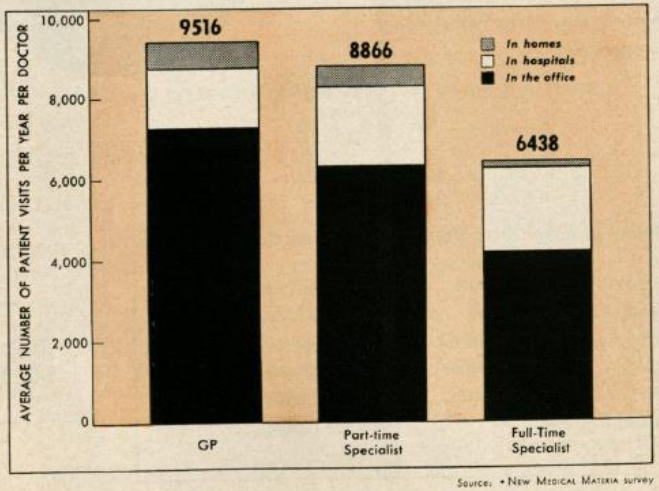
Average Doctor* Handles 154 Patient Visits A Week

*In Private Practice

WHERE THE VISITS ARE MADE



In A Year, The Average GP Takes Care Of 9500 Patient Visits



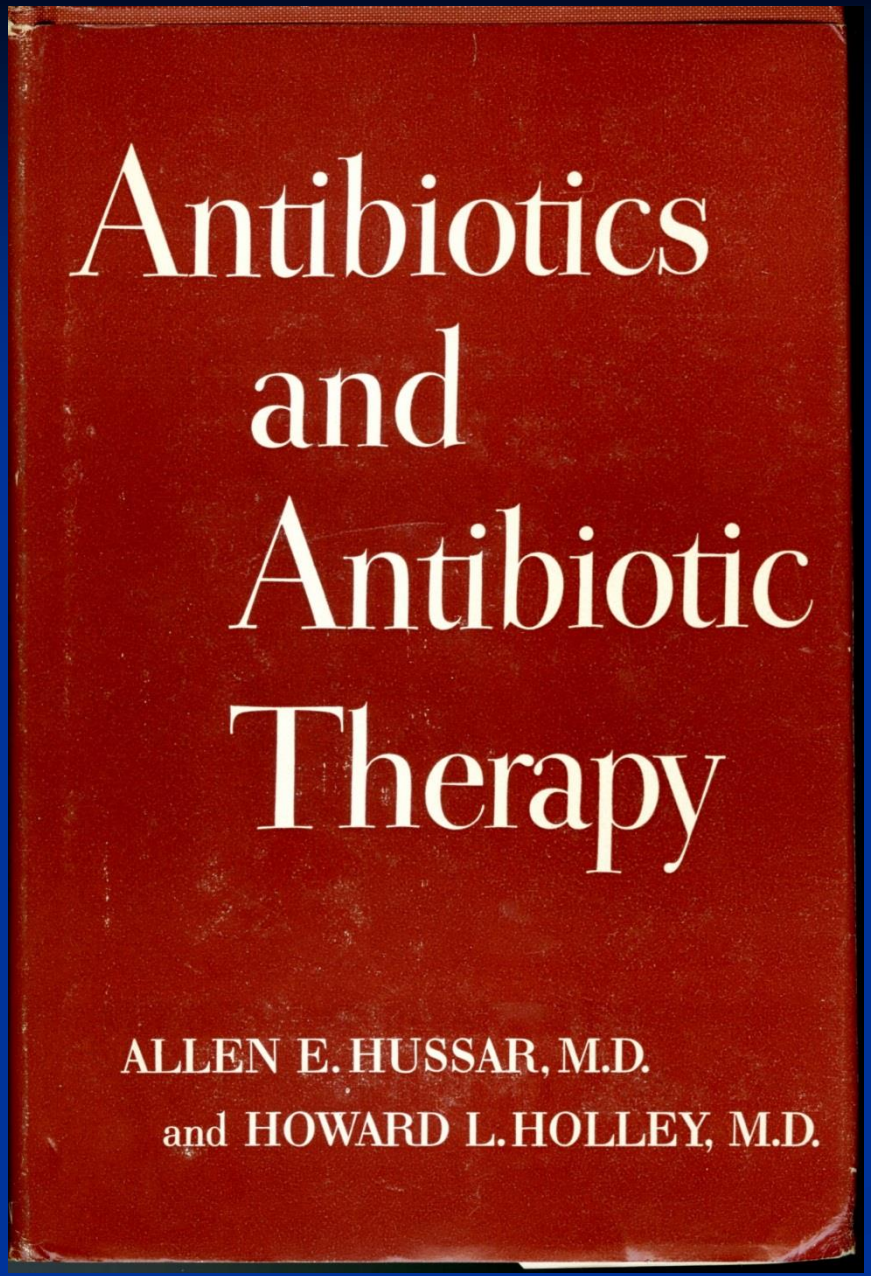
Source: • New Medical Materia survey

Prescription Writing

This record gives a 4-month comparison of all prescriptions, classified according to their primary purpose. Data represents Rxs filled by U.S. pharmacies. To ascertain per cent of all Rxs written by specialists, subtract each figure in the G.P. columns from 100%. Marked shifts in last 30 days are shown by arrows: U for Uptrends D for Downtrends

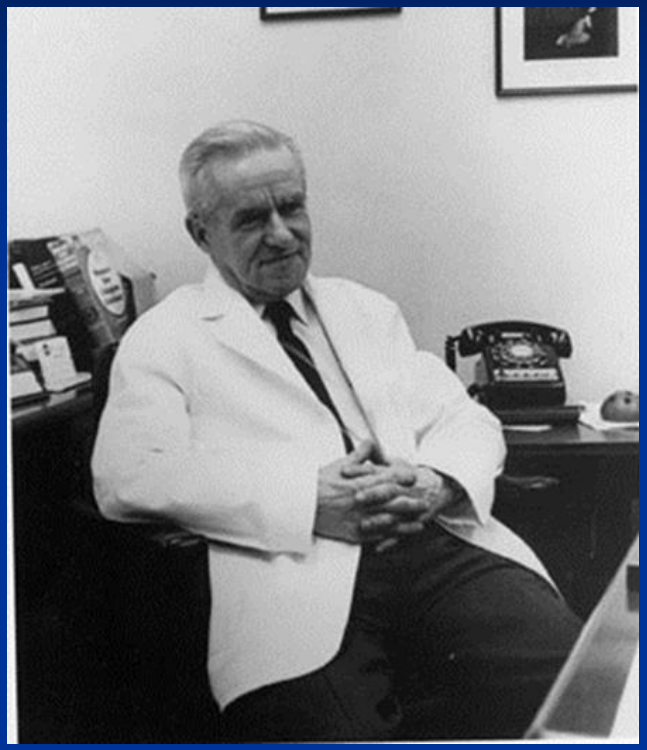
Order of Rank July Aug Sept Oct		Prescription Types	% of All Prescriptions July	Aug	Sept	Oct	% Rx Refilled July	Aug	Sept	Oct	% Written by G.P.s July	Aug	Sept	Oct
2 1 2	1	Anti-Infectives (Internal)	14.6	16.6	16.0	18.0	18.7	18.2	19.3	17.5	76.1	73.1	72.9	71.8
1 2 1	2	Sedatives, Hypnotics	16.2	14.5	16.8	15.1	59.3	59.0	58.5	58.7	76.3	76.9	76.8	78.5
3 4 4	3	Anti-Spasmodics	6.9	6.7	6.6	7.2	52.4	54.4	53.3	54.7	74.2	75.7	72.5	69.7 D
5 7 3	4	Analgesics (Internal)	6.6	5.9	6.8	6.7	22.5	21.9	22.8	22.9	74.6	75.7	78.5	75.5
4 3 5	5	Dermatologics	6.7	6.9	6.3	5.8	30.9	32.5	31.6	32.1	66.1	68.5	64.0	62.5
7 8 7	6	Metabolics	6.0	4.9	5.2	5.8	57.9	57.4	56.2	53.9	72.4	70.1	71.0	74.3
6 6 6	7	Cardiovasculars	6.6	6.2	5.5	5.6	72.1	74.0	74.5	73.8	79.9	78.1	80.0	80.1
12 11 9	8	Anti-arthritics	3.7	4.0	4.1	5.0 U	43.7	40.9	41.5	41.6	77.4	77.9	75.2	73.3
13 13 11	9	Cough Preparations	3.0	2.6	3.7	3.8	36.2	36.2	32.9	37.9 U	81.5	83.8	81.3	80.7
9 10 10	10	Stimulants	4.1	4.3	3.7	3.7	59.4	56.6	60.8	61.2	77.7	76.7	75.7	75.8
8 5 8	11	Anti-allergics	4.5	6.7	4.9	3.7 D	51.9	52.9	51.3	50.5	68.1	66.3	67.5	67.7
11 9 12	12	Diuretics	3.8	4.5	3.6	3.1	53.7	56.5	54.5	53.3	78.5	77.1	78.7	76.0
10 12 13	13	Eye Preparations	3.9	3.2	2.8	2.5	39.7	36.8	38.7	34.9 D	32.7	31.3	30.0	32.9
19 19 18	14	Cold Preparations	.8	.4	1.5	2.4	28.7	25.0	26.9	30.2	82.9	83.1	83.7	83.2
14 14 14	15	Hematinics	2.5	2.6	2.1	2.3	49.2	48.1	51.8	53.1	79.2	80.9	79.2	78.4
16 15 15	16	Sex Hormones	1.6	2.3	1.9	1.7	56.0	53.8	53.4	52.1	71.5	71.6	70.3	78.0 U
15 16 16	17	Therapeutic Vitamins	1.9	1.5	1.7	1.7	56.3	55.5	58.7	54.2	71.3	66.3	66.6	67.6
18 17 19	18	Nose Preparations	1.0	1.2	1.4	1.4	49.3	49.3	52.7	50.4	65.7	66.0	67.9	66.1
17 18 17	19	Preventive Vitamins	1.6	1.0	1.6	1.0	58.3	58.9	56.9	54.0	73.4	72.9	71.8	71.9
20 20 20	20	All Others	4.0	4.0	3.8	3.5	44.3	46.9	42.8	43.7	77.2	78.1	76.5	78.2
			100.	**100.**	**100.**	**100.**	**48.8**	**48.0**	**48.0**	**46.7**	**72.9**	**73.8**	**71.9**	**72.6**

Source: New Medical Materia



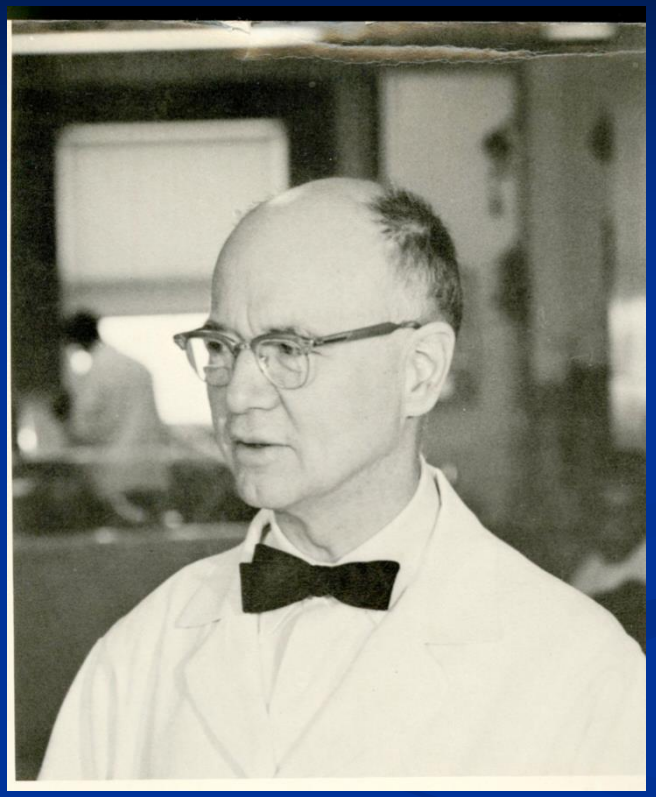
"That the patient or his family demands a 'shot of penicillin' is not the cause but the product of indiscriminate antibiotic administration."

Hussar and Holley, 1954



Maxwell Finland, 1902-1987

Image from the Countway Library of Medicine



Harry Dowling, 1904-2000

Image from *Medicines for Man* (Knopf, 1970)

Timeline of FDA Regulation

1. 1906: Food and Drug Act (purity)
2. 1938: Food, Drug, and Cosmetic Act (safety)
3. 1951: Durham-Humphrey Amendment (prescription drugs as a separate category)

ACCEPTED
COUNCIL ON PHARMACY AND CHEMISTRY
AMERICAN MEDICAL ASSOCIATION

Council accepted

new orally effective well tolerated

Terra

Active against specific organisms in the bacterial, rickettsial and protozoan groups.

Dosage: On the basis of findings obtained at over 100 leading medical research centers, 2 to 3 Gm. daily by mouth in divided doses q. 4 or 6 h. is suggested for most acute Terramycin-sensitive infections.

Supplied: 250 mg. capsules, bottles of 16 and 100.

Pfizer

Recent clinical findings indicate that:

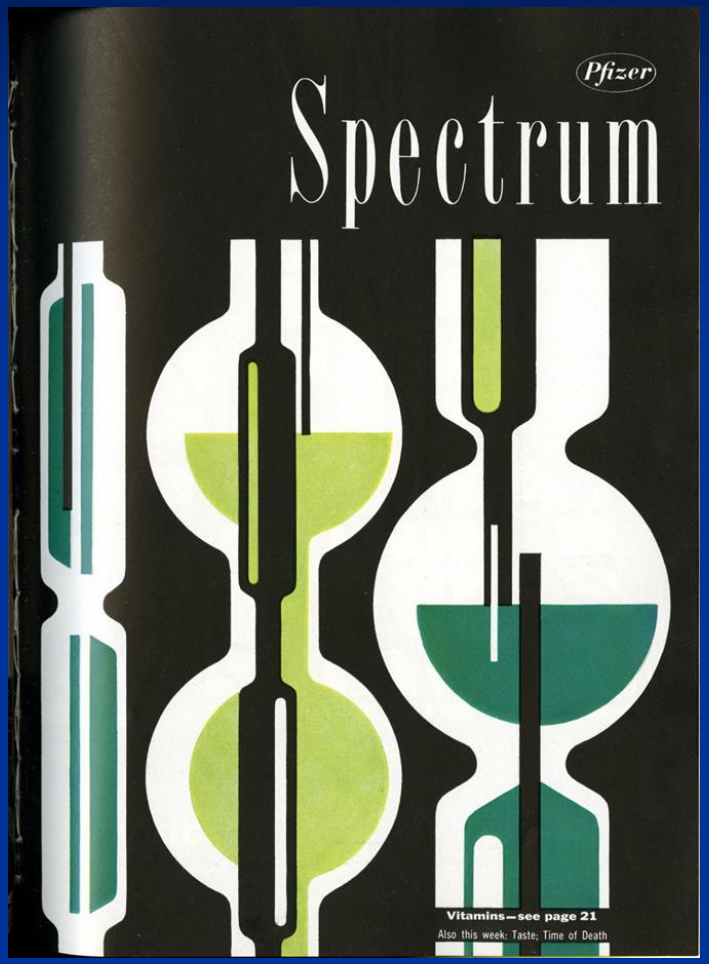
1. Terramycin may be highly effective even when other antibiotics fail.
2. Terramycin may be well tolerated even when other antibiotics are not.

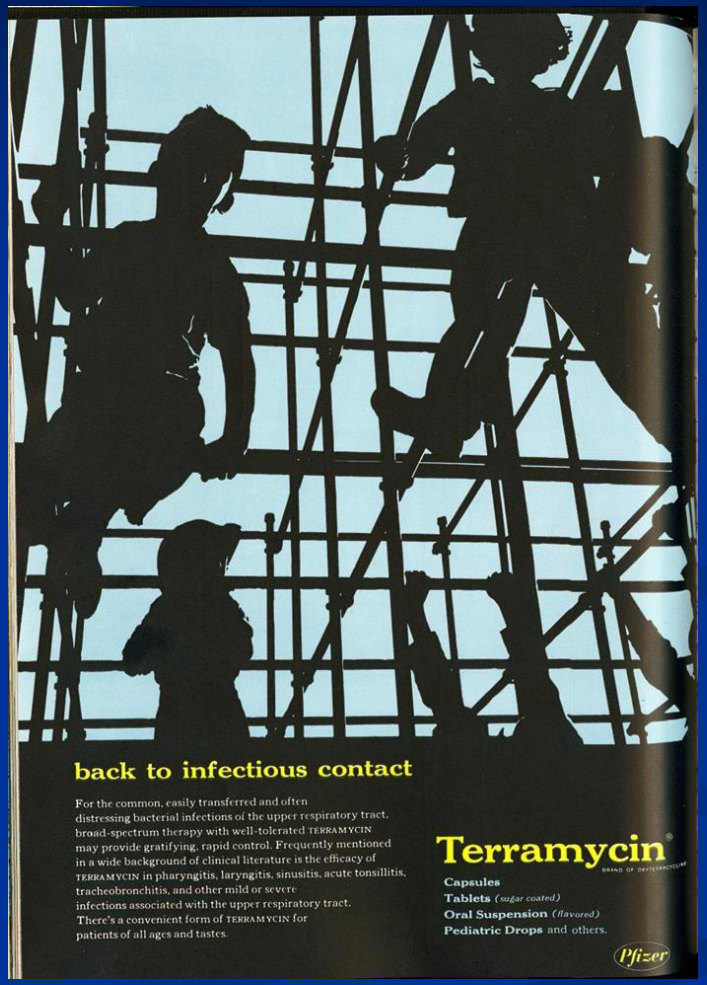
broad-spectrum antibiotic

mycin

Suggested for:

CHAS. PFIZER & CO., INC.,


Pfizer
Spectrum
Vitamins—see page 21
Also this week: Taste; Time of Death


back to infectious contact
For the common, easily transferred and often distressing bacterial infections of the upper respiratory tract, broad-spectrum therapy with well-tolerated TERRAMYCIN may provide gratifying, rapid control. Frequently mentioned in a wide background of clinical literature is the efficacy of TERRAMYCIN in pharyngitis, laryngitis, sinusitis, acute tonsillitis, tracheobronchitis, and other mild or severe infections associated with the upper respiratory tract. There's a convenient form of TERRAMYCIN for patients of all ages and tastes.
Terramycin
BRAND OF OXYTETRACYCLINE
Capsules
Tablets (sugar coated)
Oral Suspension (flavored)
Pediatric Drops and others.
Pfizer

Presidential greetings to the Antibiotics Symposium are read by (*left to right*) Dr. Henry Welch, Director, Division of Antibiotics, Food and Drug Administration, and Symposium Chairman; Sir Howard W. Florey, University of Oxford, Oxford, England; and Dr. Félix Martí-Ibáñez, Professor and Director of the Department of the History of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, who served as Moderator of the Historical Session.

Antibiotics Annual (1958-1959): xviii

have already recognized this need. Their assistance to scientific publications, by means of their advertisements, is helping to solve that vital problem of medical communication: to bring out at the *earliest* possible date, to as *many* people as possible, the *greatest* possible number of the *best* possible medical works.

A medical publication should not be an ivory tower. It should be an open forum accessible to all physicians and research workers where they may speak freely to all their colleagues. In theory as in practice, that is what I think, and that is the way I have directed the course of our modest contribution to the solution of the problem of medical communication in the field of antibiotics.

CHAIRS IN ANTIBIOTIC MEDICINE AND THE INTERNATIONAL ANTIBIOTIC INSTITUTE

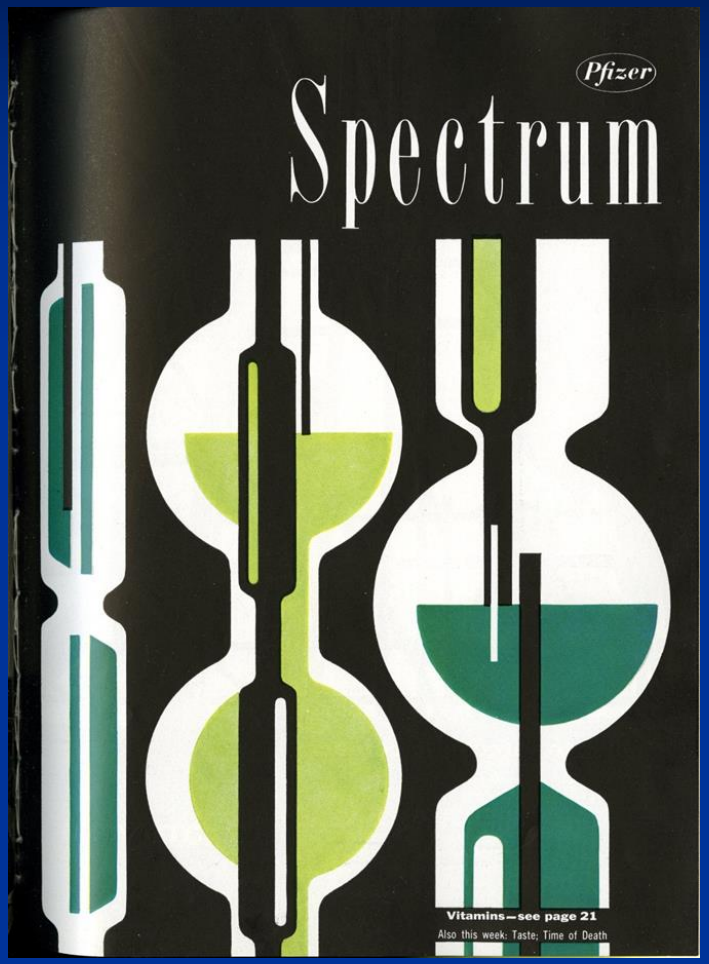
But what can one or even several publications do? A great deal more must be done and that on an international scale. Herman T. Biggs once made a statement that became the motto of the New York State Public Health Department: *"Public health is purchaseable; within natural limitations any community can determine its own death rate."* So also might we say that medical communication can be financed, and within certain limits each medical community can determine the degree of knowledge its members may attain.

Who better than the pharmaceutical industry could organize, coordinate, and integrate on an international scale the vast and increasing knowledge on antibiotics?

From this platform every year for the past three I have launched a call, which I now repeat, to the pharmaceutical industry to establish Chairs in Antibiotic Medicine in various countries of the world and to set up an International Institute of Antibiotics dedicated exclusively to organizing knowledge in this field, a center to act as a universal brain for receiving, classifying, synthesizing, and making available all printed material on antibiotics. Such an international center, by means of its publications, chairs, traveling professors, iconographies, and museums, could solve the problem of world-wide communication of antibiotic knowledge, which in turn would ensure increasing progress in antibiotic medicine.

This is no castle in Spain, no Utopian vision; it is an all-compelling necessity which will aid both the abstract science and the practical art of medicine. Such an institution might very well help the modern physician to become what more than two thousand years ago that magnificent Athenian, Plato, demanded: the medical statesman—the *Asklepios politikos*.

Antibiotics Annual (1956-1957): 14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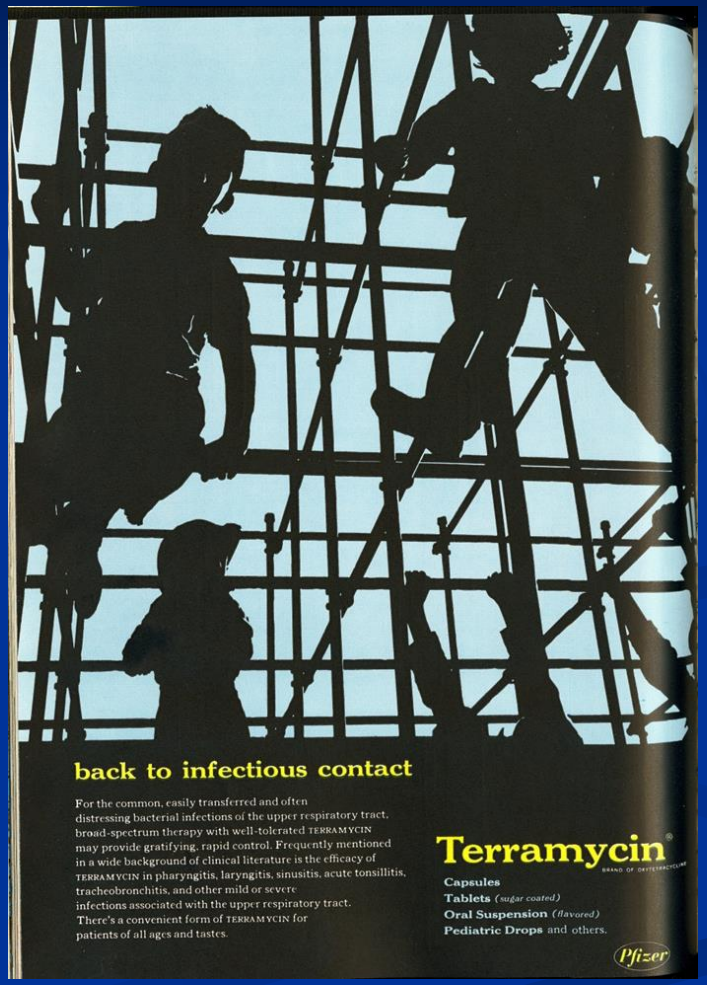
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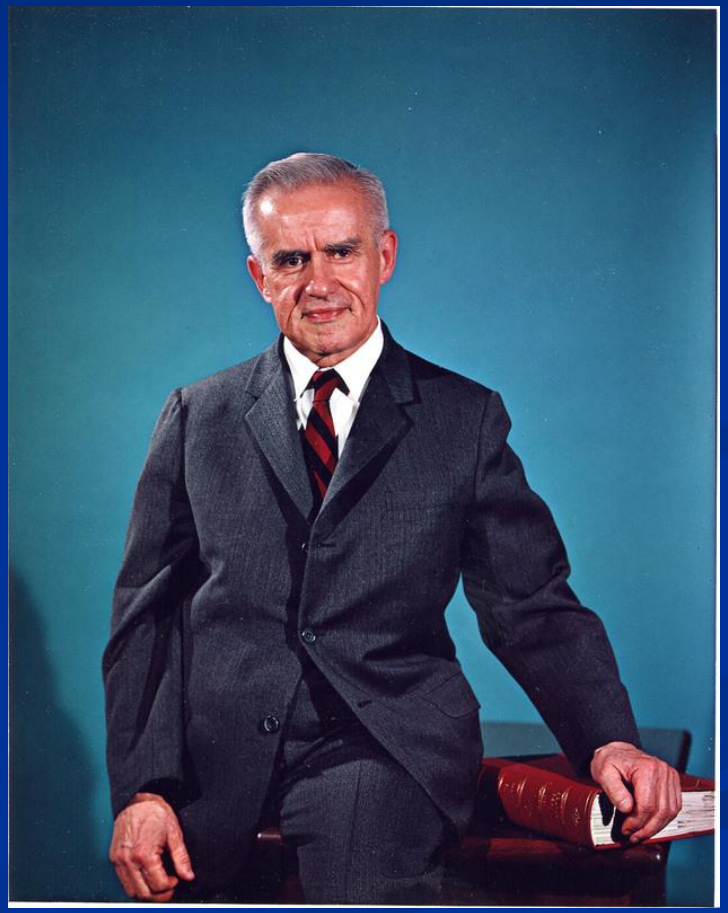
Terramycin
BRAND OF OXYTETRACYCLINE
Capsules
Tablets (sugar coated)
Oral Suspension (flavored)
Pediatric Drops and others.
Pfizer

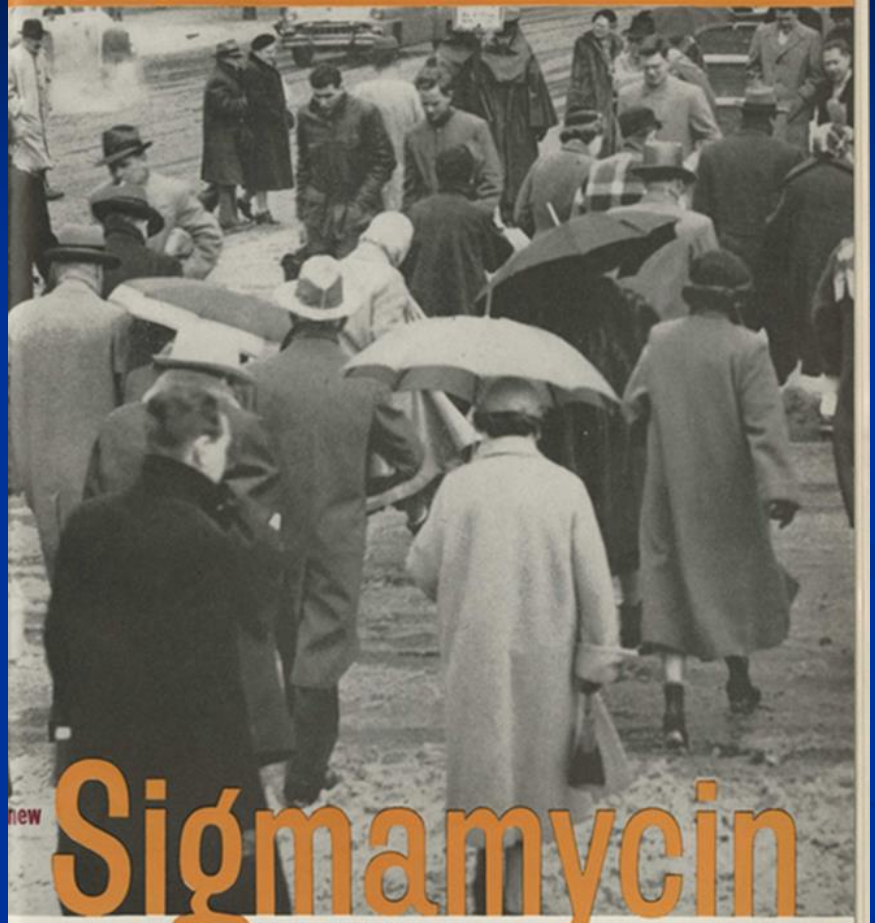
II. Antibiotics, the FDA, and the Controlled Clinical Trial

Maxwell Finland at work in the Thorndike Memorial Laboratory, early 1930s



Maxwell Finland, 1902-1987

for the 90% of the patient population treated in home or office, where sensitivity testing is not practical, synergistically strengthened multi-spectrum therapy . . .



new **Sigmamycin**

OLEANDOMYCIN TETRACYCLINE

. . . adds new certainty to treatment of infectious disease

1 a new maximum in therapeutic effectiveness

2 a new maximum in protection against resistance

3 a new maximum in safety and toleration

Pfizer

Capsules: 250 mg. (oleandomycin 83 mg., tetracycline 167 mg.).

Oleandomycin, a new antibiotic, is combined in mixtures with tetracycline, oxytetracycline, and penicillin. In addition, it is compounded with penicillin to make a penicillin salt of oleandomycin. To reduce the numbers of both gram-positive and gram-negative bacteria in the intestinal tract preparatory to abdominal surgery, oleandomycin will also be reported to be useful in combination with neomycin. Further evidence is given of the value of a combination of nystatin and tetracycline. Combinations of neomycin and novobiocin, neomycin and nystatin, neomycin and bacitracin, neomycin and chlorquinadol, neomycin and erythromycin, neomycin and oxytetracycline, and neomycin and sulfathalidine all will be discussed with respect to their increased value and extension of activity, particularly as agents valuable in preoperative preparation for abdominal surgery. These presentations and others indicate a distinct trend toward combined therapy, not an old fashioned "shotgun" approach, but a calculated rational method of attacking the problem of resistant organisms. It is quite possible that we are now in a third era of antibiotic therapy; the first being the era of the narrow spectrum antibiotics, penicillin and streptomycin; the second, the era of broad-spectrum therapy; the third being an era of combined therapy where combinations of chemotherapeutic agents, particularly synergistic ones, will be customarily used.

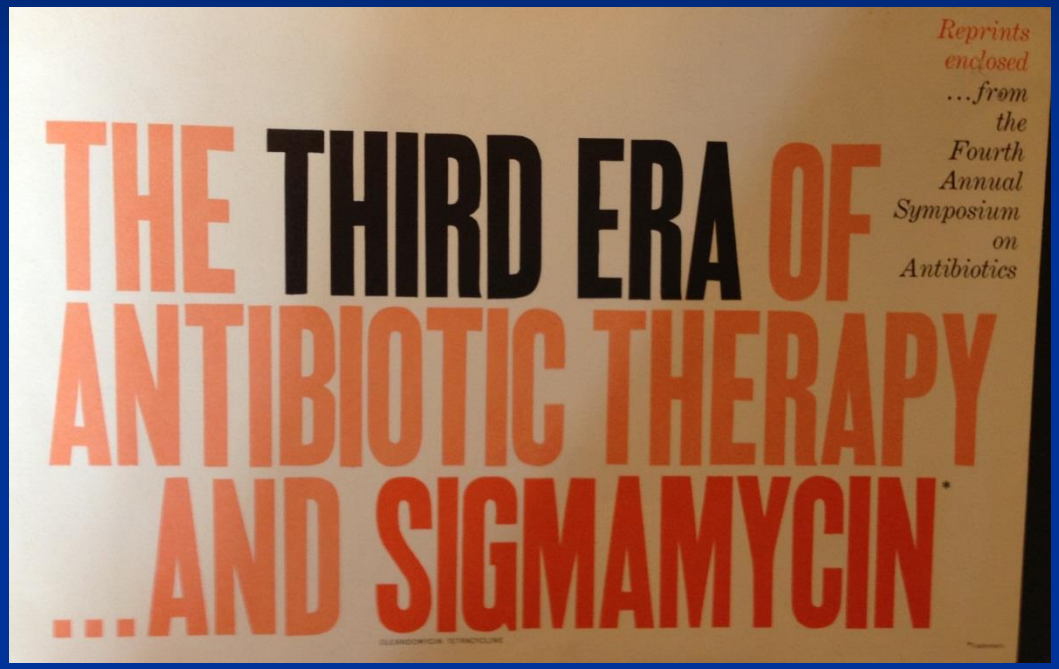
Practically an entire day will be given over to a discussion of antibiotics as food preservatives, an important economic problem of great concern to the public health. Papers will be presented concerning the use of antibiotics in maintaining the freshness of poultry, fish, beef, ham, and vegetables.

Five new antibiotics are to be described; ristocetin, PA 132, an antibiotic oil isolated from a plant, nucleocidin, and alazopeptin, the latter active against mouse sarcoma 180. More information will be made available on the relatively new antibiotics Bryamycin, vancomycin, and amphomycin. The older ones are not neglected since new studies are to be presented on erythromycin, nystatin, cycloserine, penicillin V, and synnematin B.

Again this year panel discussions are scheduled covering three important subjects: resistant staphylococci in hospitalized and nonhospitalized patients, intestinal antisepsis, and food preservation with antibiotics. All should be of considerable interest to the members of the conference.

It is now a pleasure to introduce Mr. George P. Larrick, Commissioner of the Food and Drug Administration, who has kindly consented to greet those in attendance.

Antibiotics Annual (1956-1957): 2



Pfizer Laboratories

BROOKLYN 6, NEW YORK

IN THE NEW THIRD ERA OF ANTIBIOTIC THERAPY...

Dear Doctor:

...that the medical profession is increasingly concerned with the development of antibiotic-resistant organisms is evident by the emphasis this problem received from participants in the Fourth Annual Symposium on Antibiotics. That great strides have been made toward their control is also evident from the welcoming address of Dr. Henry Welch who foresees "...a distinct trend towards combined therapy, not an old fashioned 'shotgun' approach, but a calculated rational method of attacking the problem of resistant organisms."

In discussing the history of the emergence of antibiotic-resistant organisms, and the progress being made toward their control, Dr. Welch expressed the view that it is quite possible that we are now in a THIRD ERA of antibiotic therapy: "...the first being the era of the narrow-spectrum antibiotics, penicillin and streptomycin; the second, the era of broad-spectrum therapy; the third being an era of combined therapy where combinations of chemotherapeutic agents, particularly synergistic ones, will be customarily used."

We at Pfizer are gratified to feel that our new synergistically strengthened multi-spectrum antibiotic formulation, Sigmamycin,* fulfills the criteria for advancing antibiotic treatment into this new THIRD ERA envisioned by Dr. Welch. Sigmamycin holds this distinction because it contains both the new antimicrobial agent, oleandomycin, found to be uniquely effective against resistant staphylococci, and the

*Trademark (oleandomycin tetracycline)

DIVISION, CHAS. PFIZER & CO., INC.

Maxwell Finland and Henry Welch, 1956 symposium

Maxwell Finland papers,
Countway Medical Library

UNIVERSITY OF ILLINOIS
COLLEGE OF MEDICINE
1853 WEST POLK STREET
CHICAGO 12, ILLINOIS

DEPARTMENT OF MEDICINE
840 South Wood Street

November 6, 1956

Doctor Maxwell Finland
Thorndike Memorial Laboratory
Boston City Hospital
Boston, Massachusetts

Dear Max:

Yesterday I went down to the meeting of the Council on Pharmacy & Chemistry, and presented our viewpoint on the use of antibiotic combinations. I will try to tell you what happened in the order that the things happened.

When I came in I recognized that there were a number of my friends on the committee, and whether it was from friendship or not most of the discussion was confined to these people. Doctor Sollman was presiding, and did not keep me waiting long before he called on me. I stated what the problem was, and that I thought the Council on Pharmacy & Chemistry should do its best to improve the situation. Doctor Sollman then called on Perrin Long, who stated that Doctor Stormont had just sent a note to him a few minutes before, stating that I was coming. Perrin said that as far as he knew the Council on Pharmacy & Chemistry had not accepted any combinations except triple sulphonomides and streptomycin-dihydro-streptomycin. I replied that it was not council acceptance that I was asking for, but a concerted effort to improve the situation with the council's backing. Perrin then stated that he thought that legislative changes would be very difficult to get -- that a lobby would have to be formed and that this would have to compete with the large lobby of the pharmaceutical manufacturers.

Tom Brown then stated that he understood that combinations might prevent the appearance of resistant strains, and I was called on to answer that. I stated that while there was some laboratory evidence for this, that outside the field of tuberculosis I did not feel that there was any good clinical evidence, that the only clinical report was the one that Lepper had made and that we did not think that this showed very much delay. Tom then agreed that what was needed for any of these decisions was time enough to find out what the truth was before the pharmaceutical houses began to advertise it.

Since the Food and Drug Administration had been mentioned, Dr. Holland, the Medical Director, who was there, was called upon to state what the Food and Drug Administration could do, which he did in a few words. There were a

number of questions about this, but nothing developed which you and I are now already aware of. In the course of the discussion I stated among others that I thought that the publicity regarding combinations of antibiotics at the Antibiotics Symposium was most wise. I gathered from the laugh that we got that most people agreed with this. Joe Stokes said that the problem went deeper and that doctors were treating without diagnosing; if we did anything we should also try to provide laboratory facilities so that they could do better workups. Perrin ~~and~~ Long immediately stated that laboratory work was so poor in this area that he doubted whether we should try to develop more laboratories. Doctor Ovid Meyer, Professor of Medicine in Wisconsin, spoke in favor of what I had said, and there were one or two others whom I did not know. However, the upshot of the whole thing was only that they asked me to write a status report on Combinations of Antibiotics for publication in the AMA Journal, and requested of the editor that an editorial be written for the same issue. There appeared to be absolutely no inclination on the part of the council to do anything more than that, and my feeling at the present time is that any organized movement is going to have to be done by another group.

I have not heard from Stormont yet, and he may possibly have some other ideas regarding the meeting. If so I will transmit them to you.

I should like to send you a copy of the status report for your comments when it is written, and perhaps you would want to time your editorial in the New England Journal to appear around the same time. Do you have any other ideas? We are going to bring it up at the meeting of the infectious disease group in connection with the Central Society meetings. This will take place next Friday night and I will let you know how it comes out.

I want to tell you that I think that your talk at the Upjohn meeting was excellent. I was sitting back among a number of the pharmaceutical men and although I could not hear what they said, it was obvious that they were quite interested and were making frequent comments to each other and writing notes to each other.

I would be interested to know any ideas that you got out of that meeting, and anything that you have gleaned from other people that you've talked to. I really think the time is ripe for a concerted movement, and that a lot of people will be interested in joining it. The big question in my mind is whether we should try to take some of the more ethical pharmaceutical companies in on the movement or try to do it outside of that group.

With all good wishes,

Sincerely,

Harry

Harry F. Dowling, M. D.

HFD:rdn P.S. Read your letter to Altemeier. The idea of a mtg on combinations sponsored by the Natl Res. Council is a splendid one! You should do it by all means

HF

experience who are most keenly aware of their own limitations and most willing to refer complicated cases to those in whose hands the patient's chances for survival are the greatest.

Summary

The differential diagnosis of congenital malformations of the heart in infancy requires painstaking analysis of all available data. An accurate diagnosis can be made in a high percentage of the cases in which the lesions are amenable to surgery. Infants with congenital malformations should be operated on only in centers where experienced personnel are available.

1801 K St. N. W. (6).

Dr. H. T. Bahnson gave assistance in the preparation of this report.

References

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2. Keith, J. D., and others: Transposition of Great Vessels, Circulation **7**:830-838 (June) 1953.
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TWIXT THE CUP AND THE LIP

Harry F. Dowling, M.D., Chicago

Drugs are discovered, manufactured, and tested by scientific methods. On the other hand they are produced and marketed through a blend of personal and social motives; they are prescribed by doctors with varying knowledges and skills, and they are taken by patients who have different degrees of information, interest, and precision. Drugs are brewed in the cup of science; they are drunk through a patient's lips, and "there's many a slip twixt the cup and the lip."

Scientific attention is usually turned toward the discovery of drugs; in the present paper I shall consider the path from their development to their use. As an example, let us take chlortetracycline, one of the first antibiotics to be produced by a pharmaceutical company. After screening hundreds of specimens of soil, Duggar isolated Streptomyces aureofaciens, in the fall of 1945. Its in vitro antibacterial activity was demonstrated later in the same year.

Preparation of crude concentrates that protected animals against bacterial infections required an entire year, and further purification and initiation of large-scale production required nearly two years more. It was not until September, 1948, that clinical tests were considered adequate for submission of the data to the Food and Drug Administration. Approval by this agency was granted in October, 1948, and chlortetracycline was finally marketed on Dec. 1, 1948.[1]

The development of a drug is an intricate process, involving researchers, manufacturers, clinical investigators, and many others. All of the information obtained about the drug must be brought to the practicing physician, who is the one to prescribe or administer the drug, and it is important that this information be timely and accurate. In the evaluation of new drugs, the practicing physician should do three things. First, he should learn the mechanism by which the drug works, rather than the results somebody says it will produce. By learning the generic name, the physician can understand much about the drug. Second, when asked by a patient to prescribe a drug that is not indicated, the good physician explains rather than prescribes. Last, doctors should read pharmaceutical advertisements critically, and not be hesitant to write to editors of journals as well as drug manufacturers when they question the truth. Only in these ways can the medical profession advise and assist such a dedicated organization as the Food and Drug Administration to properly judge the merits of a drug.

From the Research and Educational Hospitals and the Department of Medicine, University of Illinois.

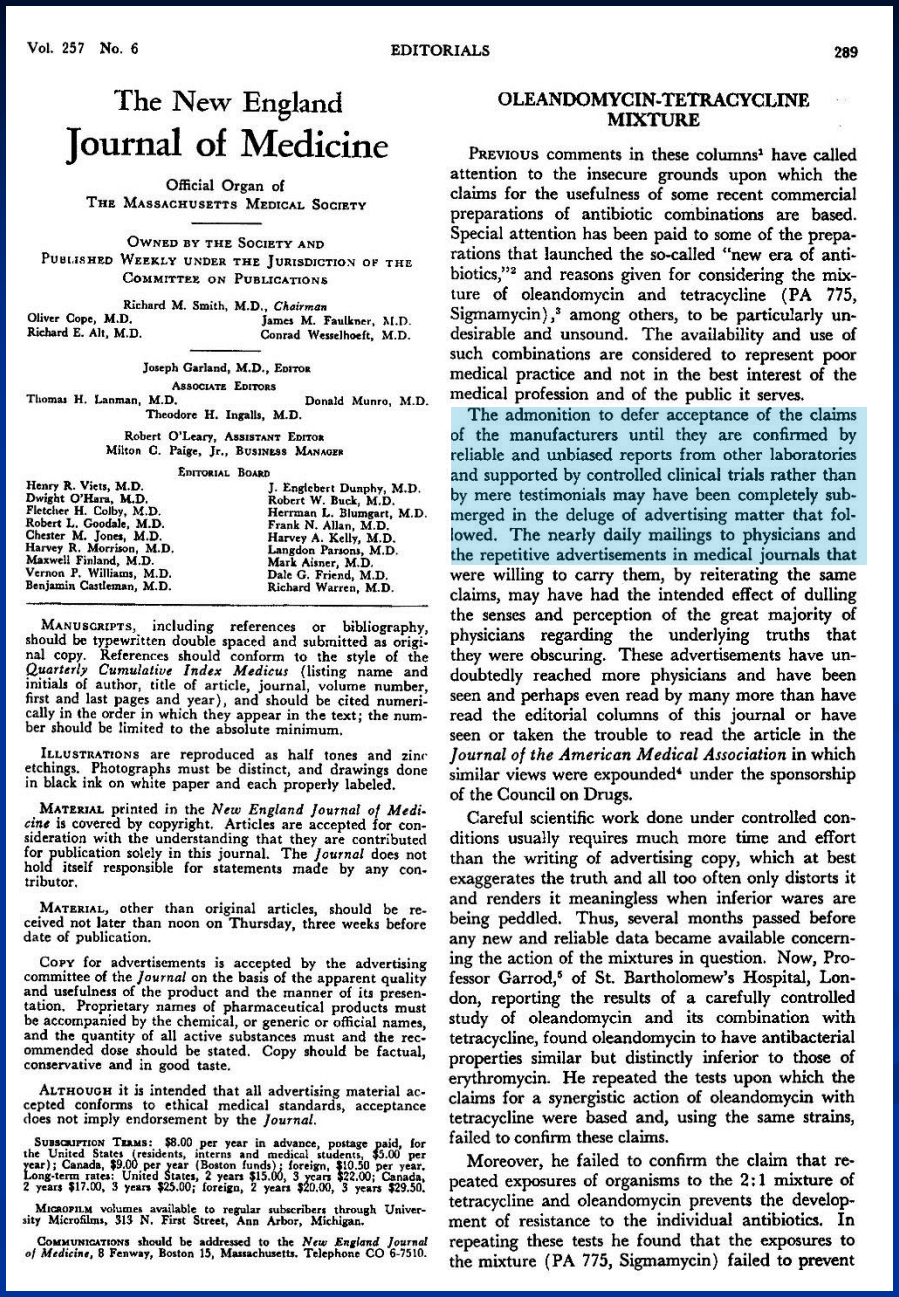
Chairman's address, read before the Section on Experimental Medicine and Therapeutics at the 106th Annual Meeting of the American Medical Association, New York, June 4, 1957.

"The techniques that had been used so successfully in the advertising of soaps … tooth pastes … cigarettes, automobiles, and whiskey [can] be used as successfully to advertise drugs to doctors. … With the inevitable disillusionment that comes with the failure of each useless modification to make any advance, the pharmaceutical industry will lose its prestige and with this will lose its financial backing. It will fall, and the medical profession will be dragged down with it."

JAMA 165 (1957): 657-61

"The admonition to defer acceptance of the claims of the manufacturers until they are confirmed by reliable and unbiased reports from other laboratories and supported by **controlled clinical trials** rather than by mere **testimonials** may have been completely submerged in the deluge of advertising material that followed."

Maxwell Finland, *NEJM 257* (1957) 289



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Although it is intended that all advertising material accepted conforms to ethical medical standards, acceptance does not imply endorsement by the *Journal*.

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OLEANDOMYCIN-TETRACYCLINE MIXTURE

Previous comments in these columns[1] have called attention to the insecure grounds upon which the claims for the usefulness of some recent commercial preparations of antibiotic combinations are based. Special attention has been paid to some of the preparations that launched the so-called "new era of antibiotics,"[2] and reasons given for considering the mixture of oleandomycin and tetracycline (PA 775, Sigmamycin),[3] among others, to be particularly undesirable and unsound. The availability and use of such combinations are considered to represent poor medical practice and not in the best interest of the medical profession and of the public it serves.

The admonition to defer acceptance of the claims of the manufacturers until they are confirmed by reliable and unbiased reports from other laboratories and supported by controlled clinical trials rather than by mere testimonials may have been completely submerged in the deluge of advertising matter that followed. The nearly daily mailings to physicians and the repetitive advertisements in medical journals that were willing to carry them, by reiterating the same claims, may have had the intended effect of dulling the senses and perception of the great majority of physicians regarding the underlying truths that they were obscuring. These advertisements have undoubtedly reached more physicians and have been seen and perhaps even read by many more than have read the editorial columns of this journal or have seen or taken the trouble to read the article in the *Journal of the American Medical Association* in which similar views were expounded[4] under the sponsorship of the Council on Drugs.

Careful scientific work done under controlled conditions usually requires much more time and effort than the writing of advertising copy, which at best exaggerates the truth and all too often only distorts it and renders it meaningless when inferior wares are being peddled. Thus, several months passed before any new and reliable data became available concerning the action of the mixtures in question. Now, Professor Garrod,[5] of St. Bartholomew's Hospital, London, reporting the results of a carefully controlled study of oleandomycin and its combination with tetracycline, found oleandomycin to have antibacterial properties similar but distinctly inferior to those of erythromycin. He repeated the tests upon which the claims for a synergistic action of oleandomycin with tetracycline were based and, using the same strains, failed to confirm these claims.

Moreover, he failed to confirm the claim that repeated exposures of organisms to the 2:1 mixture of tetracycline and oleandomycin prevents the development of resistance to the individual antibiotics. In repeating these tests he found that the exposures to the mixture (PA 775, Sigmamycin) failed to prevent

VOLUME IV NUMBER 1 JANUARY 1957

AM & CT

ANTIBIOTIC MEDICINE AND CLINICAL THERAPY

EDITORIALS

THE NEW ANTIBIOTIC ERA: FOR BETTER OR FOR WORSE?

A distinguished investigator, Dr. Maxwell Finland, has encompassed in an editorial a number of new perspectives on the subject matter of an editorial that appeared in the November, 1956, issue of this journal. We are delighted to publish this editorial by Dr. Finland, together with an editorial by Dr. Welch, which present different sides of an important research and therapeutic problem. This is in accord with our policy of publishing varied points of view in the belief that only thus can we properly advance good scientific research and good clinical practice. Regardless of whether opinions agree or not, as on all similar occasions in medical history, the final verdict on the value of a new drug or a new therapy usually comes from one dependable source: the whole body of practicing physicians whose daily clinical experiences extend over many patients treated in actual conditions of practice over considerable periods of time. Medical practice itself provides the sole and ultimate verdict on the true value of a drug, a therapy, or a medical theory.

FELIX MARTI-IBAÑEZ, M.D.

It is not unusual in a free society like ours for members of an editorial board to disagree with each other and with their editors-in-chief. In the field of pure science, such disagreements are usually best resolved by the presentation of carefully controlled data, which bear specifically on the points at issue. However, a number of clinical investigators who are intimately interested in the proper evaluation and use of antibiotics, including several members of this editorial board, have been deeply concerned about the interpretations and the immediate and broad implications of some recent trends in the use of antibiotic combinations and of the manner in which these are being exploited. These investigators felt that their opinions, too, should be heard and the editor-in-chief, with whose scientific opinions they do not often have occasion to differ, has consented to publish this editorial, which represents the joint expression of a number of these investigators.*

The opening remarks at the Fourth Annual Symposium on Antibiotics, and an editorial in the November, 1956, issue of this Journal recounted recent events which point to a strong trend toward the use of antibiotics in combinations and indicated that this was a rational and inevitable development that was ushering in a new antibiotic era. Since these remarks emanate from an outstanding authority in the field and were made specifically in relation to the presentation of a series of papers dealing with certain new combinations of antibiotics that had been compounded in specific dosage forms, they must inevitably be

* These investigators include William P. Boger, Ivan L. Bennett, Jr., Harry F. Dowling, Maxwell Finland, Morton Hamburger, William L. Hewitt, Ernest Jawetz, Edwin D. Kilbourne, Vernon Knight, Perrin H. Long, Walsh McDermott, Lowell A. Rantz, David E. Rogers, Wesley W. Spink, Ralph Tompsett, Louis Weinstein, Robert I. Wise, W. Barry Wood, Jr., and Theodore E. Woodward.

Saturday Review

JANUARY 3, 1959 / 25¢

SR/RESEARCH SCIENCE & HUMANITY

DOCTORS AND ANTIBIOTICS

Taking the Miracle Out of Miracle Drugs

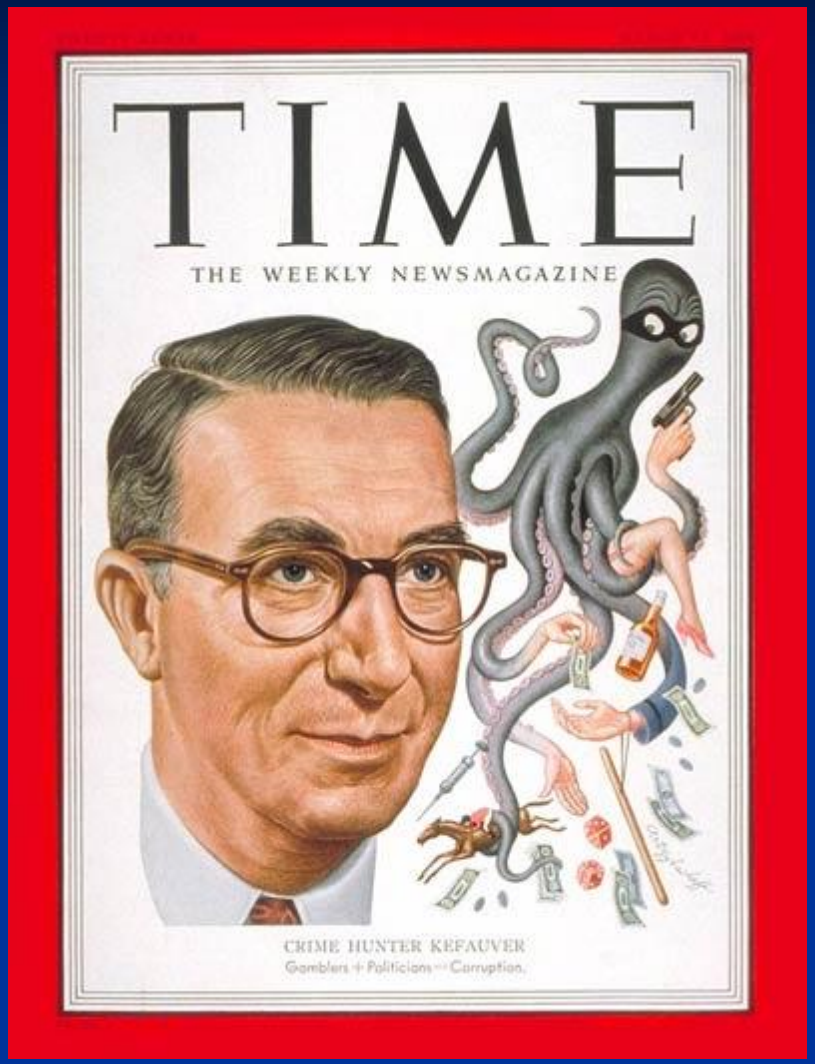
By John Lear

Arthur Schlesinger, Jr. author of "The Coming of the New Deal." ►

(See Page 15)

THE ROAD TO BERLIN

An Editorial



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© *Time*, 3/24/52

FDA Official Is Fired After Pay Disclosure

By Bernard D. Nossiter
Staff Reporter

Health, Education and Welfare Secretary Arthur S. Flemming yesterday fired Dr. Henry Welch, director of the Food and Drug Administration's Antibiotics Division.

Fleming acted after Senate investigators disclosed Welch collected $287,142.40 from outside medical publishing jobs. Most of this income was tied directly to promotion outlays by drug companies, the Antitrust and Monopoly Subcommittee was told.

Flemming declared that Welch had "deliberately misled his superiors" by taking pay "far beyond what is the concept of an honorarium for editorial services—particularly when this compensation was directly related to drug firms' promotion.

Welch, ill with a heart attack that had excused him from testifying before the Senators, last week asked to retire on June 1.

But Flemming demanded his "immediate resignation." This will not affect Welch's pension. However, if he does not resign, Flemming said he would press charges against him.

The Secretary recalled that he had merely ordered Welch to drop his outside work last October. He said he was sorry that he had not examined Welch's explanation that officials had approved his private posts in the past.

Welch's deals from 1953 to 1960 added $13,000 to $50,000 a year to his $17,500 Government pay, the Senate investigators heard.

Chairman Estes Kefauver (D-Tenn) said, "It seems to be very difficult for Welch to dissociate his official capacity from his financial interests in these (outside) publication."

He said he would call Flemming and FDA Commissioner George P. Larrick to review Welch's Government actions.

The bulk of his income, the inquiry heard, came from editing two antibiotics journals owned by M. D. Publications, Inc. of New York City. The testimony showed that an unwritten arrangement gave Welch fixed shares of the profits on reprints of articles bought largely by drug firms, articles inserted after the magazines' deadlines and their ads.

A General Accounting Office aide, Francis N. Engelstad, presented this summary of Welch's pay based on records of M. D. Publications:

- $173,000 from reprints, a 50 per cent share.
- $20,000 from advertisements, a 7.5 per cent share.
- $9700 from late insertions, a 25 per cent share.
- $1700 in commissions from bulk sale of the magazines.

With this formula, Kefauver remarked, Welch could "figure to the penny" his income loss from an "adverse action."

In addition, Engelstad said Welch took in $18,900 from a short-lived journal that drew most of its revenue from a $100,000 grant by Parke, Davis & Co. Another $63,000, the accountant testified, represented Welch's half-share in a medical publishing house.

At the same time on his Government job, Welch was testing the purity and strength of some of the companies' antibiotics and he was advising FDA on the licensing of new antibiotics.

In 1920, Welch's superiors approved his outside eidting after he wrote them, "I may receive yearly honorariums" if the magazines make money.

Webster's New International Dictionary defines an honorarium as "an honorary payment or reward, usually in recognition of gratuitous or professional services on which custom or propriety forbids any fixed business price to be set, or for which no payment can be enforced at law."

Sen. John Carroll (D-Colo.) said the "tremendous sums" Welch got couldn't be called honorariums. But Welch's lawyer, Michael F. Markel, insisted that they were because there was no legally enforceable agreement to pay them.

Welch's successor as editor of the two antibiotics magazines, Dr. Lawrence Putnam of George Washington University, is receiving $250 an issue or $6000 a year.

M. D. Publications has also been paying Dr. Winfred Overholser, superintendent of St. Elizabeth's Hospital, about $600 a year since 1955 to edit the Quarterly Review of Psychiatry and Neurology. Secretary Flemming said HEW has known of this but, in the light of the hearings, will take another look at the arrangement.

The inquiry also heard that some drug makers had questioned the propriety of Welch's outside work.

Oleandomycin, a new antibiotic, is combined in mixtures with tetracycline, oxytetracycline, and penicillin. In addition, it is compounded with penicillin to make a penicillin salt of oleandomycin. To reduce the numbers of both gram-positive and gram-negative bacteria in the intestinal tract preparatory to abdominal surgery, oleandomycin will also be reported to be useful in combination with neomycin. Further evidence is given of the value of a combination of nystatin and tetracycline. Combinations of neomycin and novobiocin, neomycin and nystatin, neomycin and bacitracin, neomycin and chlorquinadol, neomycin and erythromycin, neomycin and oxytetracycline, and neomycin and sulfathalidine all will be discussed with respect to their increased value and extension of activity, particularly as agents valuable in preoperative preparation for abdominal surgery. These presentations and others indicate a distinct trend toward combined therapy, not an old fashioned "shotgun" approach, but a calculated rational method of attacking the problem of resistant organisms. It is quite possible that we are now in a third era of antibiotic therapy; the first being the era of the narrow spectrum antibiotics, penicillin and streptomycin; the second, the era of broad-spectrum therapy; the third being an era of combined therapy where combinations of chemotherapeutic agents, particularly synergistic ones, will be customarily used.

Practically an entire day will be given over to a discussion of antibiotics as food preservatives, an important economic problem of great concern to the public health. Papers will be presented concerning the use of antibiotics in maintaining the freshness of poultry, fish, beef, ham, and vegetables.

Five new antibiotics are to be described; ristocetin, PA 132, an antibiotic oil isolated from a plant, nucleocidin, and alazopeptin, the latter active against mouse sarcoma 180. More information will be made available on the relatively new antibiotics Bryamycin, vancomycin, and amphomycin. The older ones are not neglected since new studies are to be presented on erythromycin, nystatin, cycloserine, penicillin V, and synnematin B.

Again this year panel discussions are scheduled covering three important subjects: resistant staphylococci in hospitalized and nonhospitalized patients, intestinal antisepsis, and food preservation with antibiotics. All should be of considerable interest to the members of the conference.

It is now a pleasure to introduce Mr. George P. Larrick, Commissioner of the Food and Drug Administration, who has kindly consented to greet those in attendance.

NATIONAL ACADEMY OF SCIENCES - NATIONAL RESEARCH COUNCIL
2101 Constitution Avenue
Washington 25, D. C.

Division of Medical Sciences

Special Committee Advisory to
The Secretary of Health, Education, and Welfare
To Review the Policies, Procedures, and Decisions of
The Division of Antibiotics and the New Drug Branch of
The Food and Drug Administration

9:30 A. M. - 28 June 1960
Academy-Research Council Building
Washington, D. C.

ATTENDANCE

Committee:

Dr. C. Phillip Miller, Chairman
*Dr. John H. Dingle
Dr. Maxwell Finland
*Dr. Colin M. MacLeod
*Dr. Karl F. Meyer
Dr. John R. Paul
Dr. Carl F. Schmidt
Dr. Wesley Spink

Department of Health, Education, and Welfare:

Secretary Flemming
Mr. M. Allen Pond, Staff Assistant to the Secretary

Food and Drug Administration:

Mr. John L. Harvey, Deputy Commissioner
Mr. W. B. Rankin, Assistant to the Commissioner
Mr. Frank Clark, Assistant to the Deputy Commissioner
Dr. William H. Kessenich, Medical Director, Bureau of Medicine
Mr. Robert S. Roe, Director, Bureau of Biological and Physical Sciences
Dr. Donald C. Grove, Acting Director, Division of Antibiotics

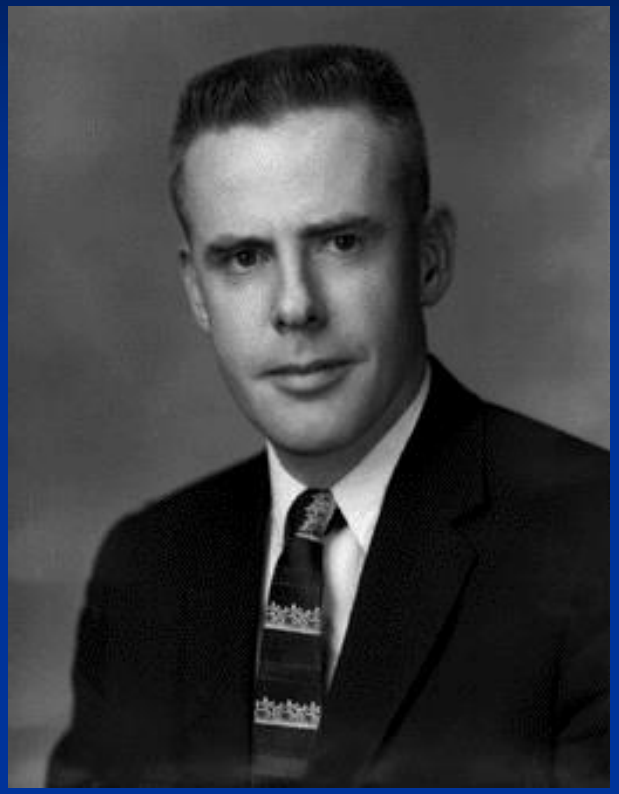
National Academy of Sciences-
National Research Council:

Dr. S. Douglas Cornell, Executive Officer, NAS-NRC
Dr. R. Keith Cannan, Chairman, Division of Medical Sciences
Mr. Herbert N. Gardner, Professional Associate, Division of Medical Sciences

*Not expected to attend

“Substantial” proof of efficacy, based on “adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved.”

Kefauver-Harris Drug Amendments, 1962



James Goddard, 1923-2010
(Source: FDA)

NATIONAL ACADEMY OF SCIENCES–NATIONAL RESEARCH COUNCIL

INTER-OFFICE MEMORANDUM

TO: For the Record DATE: 28 March 1966

FROM: R. Keith Cannan RKC

SUBJECT: Conference with Dr. Goddard and Dr. Don Estes (Management Consultant)

FDA wishes to have an evaluation of the question whether 3000 drugs approved prior to 1962 have any therapeutic value. These drugs can be broken down into about 50 categories, and the 50 categories can be further combined in 10 or a dozen groups. Probably 80% of them are quite straight forward and an answer can be given without much study. The remainder may involve differences in judgment. FDA would like a brief bibliography to support each decision.

We agreed that there seemed to be no other organization capable of doing this job and we agreed that FDA, under law, is required to do it. On the other hand FDA cannot staff up a temporary job like this.

FDA promised to send me 25 copies of a two-page statement of the task they wish undertaken, suggestions on how they would have done it and a target date for its completion. They promised this in time for the Drug Research Board meeting on Friday. They would like a proposal before the end of April so that they can commit funds. They seem to have plenty of money to spend on it. The target date seems to be something like the end of 1967. They said they hoped the job could be started in the calendar year '66. Goddard said he would not question conflict of interest in any individual selected by us.

Goddard promised staff help from FDA.

RKC/th

Archives of the National Academy of Sciences

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SPECIAL ARTICLE

FIXED COMBINATIONS OF ANTIMICROBIAL AGENTS*

National Academy of Sciences – National Research Council Division of Medical Sciences Drug Efficacy Study

Abstract A review of the claims put forward for the use of penicillin-sulfonamides, penicillin-streptomycin and certain other fixed combinations of antimicrobial agents has convinced five panels organized under the auspices of the National Academy of Sciences – National Research Council that such combinations are "ineffective as fixed dose combinations." Although the individual active ingredients may be useful in specific entities, no greater effectiveness can be expected for the combination than for any one ingredient. Use of a proper dose of one ingredient may require excessive or inadequate doses of the other. It is the judgment of the panels that the use of these fixed combinations should be discontinued and that the physician should use the individual components according to his best clinical judgment.

THE Drug Amendments of 1962 to the Federal Food, Drug and Cosmetic Act of 1938 fix requirements for the effectiveness as well as the safety of drugs. As an aid to the Food and Drug Administration (FDA) in this formidable task of evaluation, the National Academy of Sciences–National Research Council (NAS–NRC) undertook the Drug Efficacy Study in 1966 under contract (FDA 66-197 [Neg.]) with the FDA. Essentially, the NAS–NRC agreed to review the claims for effectiveness of drugs approved between 1938 and 1962 and to rank each claim for each drug for its degree of effectiveness. Reports embodying the recommendations of the Study have recently been submitted to the FDA.

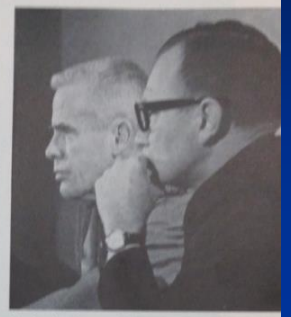
The Study was conducted by a group of 30 panels, each consisting of a chairman and five additional members. Policy guidance was provided by a Policy Advisory Committee consisting of 22 members. Four of the 30 panels (anti-infective panels I-IV) were concerned primarily with the use of antimicrobial agents for indications other than tuberculo-

*This report was prepared by Anti-infective Panels II and IV of the Drug Efficacy Study, Division of Medical Sciences, NAS–NRC; the chairmen of these panels are Dr. Calvin M. Kunin and Dr. William L. Hewitt. Subsequently, the report was circulated to Anti-infective Panels (I, III and V) and was approved by the respective chairmen: Dr. Heinz Eichenwald, Dr. William M. M. Kirby and Dr. William B. Tucker. In its present form, therefore, the report has approval of all Anti-infective Panels of the Drug Efficacy Study. Members of Panel II are Drs. William McCabe, John Nelson, Edward L. Quinn, Jay P. Sanford and Ian Maclean Smith. Members of Panel IV are Drs. M. Glenn Koenig, Floyd W. Denny, Sidney M. Finegold, Donald B. Louria and Arthur C. White.

Address reprint requests to the Drug Efficacy Study, Drug Research Board, National Academy of Sciences–National Research Council, 201 Constitution Ave., N.W., Washington, D.C. 20418.

NEJM, 5/22/69

THE 'NEW' LEY BARES FDA TEETH



Dr. Ley's takeover of FDA from Goddard (left) seemed to herald a period of quieter, more deliberate regulation.

Dr. Herbert L. Ley Jr. is ending his first year at the helm of the Food and Drug Administration a man transformed. The dark-haired, bespectacled, 45-year-old epidemiologist began his duties as commissioner last July 1 on a note of quiet caution, and he held that note throughout the first half-year of his reign. But now he has taken to publicly castigating the pharmaceutical industry and has committed himself to a war on fixed-combination drugs. In its latest move, his agency has ordered 49 combination antibiotics off the market.

Why this turnabout, this seeming switch from a mild-mannered Dr. Jekyll to a fire-breathing Dr. Ley? And just how profound is the change?

"If you want to find motivation for what appears to be and is, I admit, a somewhat firmer public voice," says the commissioner, "you don't have to look further than the past five or six months of industry response to the National Academy of Sciences–National Research Council efficacy review of drugs marketed before 1962. The degree to which it has resisted what I considered a pretty fair and reasonable course came as somewhat of a surprise."

But for all that surprise, there is little doubt that pressure from Capitol Hill—particularly from Rep. L. H. Fountain (D-N.C.) and his House Intergovernmental Relations Subcommittee—was instrumental in developing the commissioner's "firmer public voice." Those pressures have been intense. Last April, when Dr. Ley was called to tell the Fountain panel why he had waited ten months before ordering mislabeled stocks of parenteral chloramphenicol sodium succinate off the market (MWN, May 16), he didn't handle the harsh interrogation well. "I think this thing really damaged him greatly," says Dr. Walter Modell, professor of pharmacology at Cornell Medical College.

Dr. Ley's performance on the Hill raised perhaps another factor — or specter — relating to his transformation: the prospect of losing his prestigious $36,000-a-year job. After the April hearings, reports were circulated that HEW Secretary Robert Finch was taking a long second look at the man he had inherited and retained as FDA chief. At that point, remarked one observer, "Herb got religion."

He also apparently assured himself a job. According to a top HEW official, "Everyone thinks Dr. Ley is doing a great job. There are no plans to recruit a new commissioner. Especially in the past few weeks he has moved hard and swiftly to protect the public."

If there was a turning point in Dr. Ley's career, those hearings were it. In early May, he announced an end to the FDA's approval of new batches of *Panalba* (Upjohn), a mixture of tetracycline and novobiocin, on safety grounds and ordered it off the market by June 14. Upjohn then won a restraining order until June 20, plus a federal court hearing on that date.

Then, earlier this month, Dr. Ley issued similar bans against the marketing of 48 combinations of penicillin and streptomycin and of penicillin and sulfa for reasons of both inefficacy and potential hazard. He also ordered Squibb's *Mysteclin F*, an antibiotic combining tetracycline and amphotericin B, removed from the market unless the producer could demonstrate effectiveness in an FDA hearing.

Combination drugs have not been the only targets. Dr. Ley has requested a hearing on the effectiveness of *SERC* (Unimed), a drug used to counter the effects of vertigo in Ménière's syndrome, before barring it from the market, has banned further sales of Dr. Scholl's ingrown-toenail remover, *Oxinol*, on grounds of inefficacy, and has even rung the gong on Hawaiian Punch by ordering fermented stocks withdrawn. He has also severely scolded Abbott Laboratories for keeping cracked bottles of parenteral solutions — sugar and salt solutions and distilled water — on the market for months despite reports of patients' reactions to possible contamination.

Dr. Ley will not attribute these regulatory actions to pressure from the Fountain subcommittee, though he concedes that congressional hearings have shown him that he has to be more hard-nosed. In testifying that he did not take those mislabeled stocks of chloramphenicol sodium succinate off the market because he felt physicians should have access to the drug, Dr. Ley was clearly misinterpreting the letter of the law. The commissioner, says Dr. Modell, "found himself in an unsupportable position."

Recalling those Fountain panel sessions, Dr. Ley says: "What the committee has done is to make clear to the FDA — and, more specifically, to me — that it expects us to move to the full limit the law permits."

It's no secret that the drug industry thought it was in for an easier time when Dr. Ley took over FDA from James Goddard, regarded as a crusading swashbuckler by congressional backers and as a shoot-from-the-hip-

continued

1961). This is an in vitro study of bacterial sensitivities during a 6-month period. All organisms were not tested against each antibiotic, nor were antibiotics tested against organisms to which they were known to be resistant.

51. *Johnson, F. T., et al. Effect of a Novobiocin-Sulfonamide Combination on Organisms Generally Associated with Urinary Tract Infections, Antibiotics Annual 1957–58: 27–30.* This paper reports a bacteriologic study on the in vitro activity of novobiocin, sulfamethizole, and the combination, on four strains of gram negative bacteria. Each of these strains was then made resistant to each of the antimicrobial agents. In vitro studies were then done, showing the effect of each agent alone and in combination. As expected, growth occurred in media containing the drug to which the bacteria had been made resistant, but not in media containing the drug to which the organism was still susceptible. In these situations, growth did not occur when the combination was employed. This result is to be expected, since the drug to which the bacteria remained susceptible was capable of inhibiting growth rather than the combination.

These in vitro studies are not clinical data, are not correlated with clinical data, and may not be extrapolated to the clinical situation involved in treating infectious disease in the United States. The data submitted are inadequate in many details, as has been noted, and permit no conclusions to be drawn because of the deficiencies noted. All that the data could reasonably be taken to show is that some infectious organisms encountered in disease situations are susceptible in vitro to equal amounts of novobiocin and tetracycline. But whether the tetracycline or the novobiocin was responsible is not established.

(c) *Animal study.* A single study of the use of the combination of novobiocin and tetracycline to treat an experimental infection in the mouse was submitted by the firm.

16. *Pecori, V., et al., Preliminary results on the efficiency of the association of novobiocin-tetracycline in staphylococcal infection in the mouse. Boll. Soc. Ital. Biol. Sperim. 34 : 534–536 (1958).* This is a poorly designed experimental study using groups of white mice inoculated with stephylococci. It is not possible to extrapolate the results of this study in mice to the therapeutic situation in man.

(2) *Studies evaluating clinical response in man*—(A) *Uncontrolled studies of the Tetracycline-Novobiocin Combinations.* The Commissioner has considered and reviewed the remaining investigations listed by Upjohn, and finds as follows:

2. *Abbott, M. I. and Riley, H. D., Jr., Treatment of Staphylococcal Infections in the Young Infant with Tetracycline and Novobiocin in Combination. Antibiotic Medicine and Clinical Therapy, 8:23–28 (January 1961).* This is a report of treatment with Panalba KM Granules (pediatric) of 28 infants, aged 1 day to 5 weeks, 25 of whom had staphylococcal infections verified by culture, and two of whom had streptococcal infections. Two infections showed no response. Doses given varied widely. This study was not controlled. Only the combination product was used. The study presents no evidence that the combination product is better than either drug alone. In vitro susceptibility study showed that all staphylococcal strains isolated from the patients and subjected to susceptibility studies were susceptible to novobiocin alone.

3. *Anderson, Jack R. and Rubin, Wallace, Clinical Experience with Combined Tetracycline Novobiocin Therapy in Common Ear, Nose and Throat Infections. The Eye, Nose and Throat Monthly 38: 638–641, 1959.* 95 patients, adults and children, with ear, nose, and throat infections were treated with Panalba capsules or liquid, administered four times daily for 4–10 days. Sinusitis cases were additionally treated with local novobiocin instillation and 62 of the patients received concomitant antihistamine therapy. It is impossible to tell what if any improvement is attributable to novobiocin instillation and/or antihistamine therapy.

Cultures were taken from some of the patients. The only result reported was that 47 of the first 50 cultures taken revealed the organisms to be sensitive to the tetracycline-novobiocin combination. Sensitivities to tetracycline or to novobiocin alone are not reported. This study is poorly designed and not controlled. It presents no evidence that the combination product is effective or that it is more effective than either drug alone.

5. *Atkins, J. L., Novobiocin-Tetracycline in the Treatment of Ear, Nose and Throat Infections. Canadian M.A.J. 83: 909–911 (Oct. 22, 1960).* This report involved Albamycin-T (tetracycline-novobiocin in equal parts) using two preparations, tablets and granules for suspension. The author, citing data from a personal communication, reports an in vitro test of four organisms (two strains of M. aureus, one of P. rettgeri, one of S. fecalis), said to show "enhancement of antimicrobial activity when tetracycline and novobiocin are combined in the ratio of 10 parts of novobiocin to 1 part of tetracycline." This is a laboratory exercise having no clinical applicability. Moreover, no such 10:1 combination has ever been marketed, and the dosage cannot be achieved by using the combination.

In addition, the author presents the following clinical report: 80 patients with ear, nose, and throat infections were treated with a dose of 1 gm. of the combined antibiotics per day for the adults, and "at least 15 mg. of the combined antibiotics per kg. body weight per day" for children. 82 percent of the infections were streptococcal in origin. No sensitivity tests or follow-up cultures were done. Duration of treatment is not stated. There were two adverse reactions of the type known to be associated with novobiocin. Novobiocin is not indicated in streptococcal infections. This report states that most of the patients responded to the combination, but no controls were used. There is no evidence to show that the combination is effective or that it was better than that which might be expected from tetracycline alone.

6. *Baadj, A. G., Loperfido, F. J. and Prigor, A., Treatment of Soft-Tissue Infections in Children with an Antibiotic Combination, Tetracycline and Novobiocin with Metaphosphate. Antibiotic Med., 5 : 664–668 (November 1958).* This is a report of 50 cases of soft-tissue infections in children, treated with "Panalba flavored granules" (125 mg. of tetracycline and 62.5 of novobiocin in 5 ml. of suspension). There is a list of strains of microorganisms isolated, from the lesions "whenever pus or exudates were recoverable". These cultures are not related to specific cases. The therapeutic results were said to be good, but there were no controls and no evidence to indicate that the combination was better than what would be expected from either of the antibiotics had they been used alone. In addition, the infections were of such a nature that improvement might been been expected without antibiotic therapy.

8. *Boissier, A. et al., Efficacite de L'Association Novobiocine-Tetracycline Dans le Traitement et al Prevention des Surinfections de la Bronchite Chronique. La Vie Medicale Actualite, Dec. 1966; 29–30.* Forty-five patients with respiratory insufficiency resulting from chronic bronchitis were treated with "Albacycline," in a total daily dose of 500 mg. each of tetracycline and novobiocin for from 6 to 47 days; the average was 16 days. Sixteen of the cases were concomitantly treated with corticosteroids. Good results were achieved in 23 patients, 12 fair, and 10 negative. No cultures were made, and there were no controls. The study is not related to Upjohn's claims.

10. *Chesrow, E. J., et al., Clinical Evaluation of Tetracycline-Novobiocin on 100 cases of Acute Infection Due to Staphylococci and Other Bacteria. Antibiotic Med. 7: 490–494 (August 1960).* One hundred patients with various infections were selected at random. Panalba was the product used, one capsule being given every 8 hours. Diagnoses listed were: Carbuncles, abscesses with cellulitis, pneumonia, tonsillitis, cystitis, otitis. Organisms cultured were: Staph. aureus (80 cases), betahemolytic Streptococcus (3 cases), Proteus mirabilis (5 cases), Escherichis coli (5 cases), Hemophilus influenzae (2 cases), Pseudomonas (3 cases), and gammahemolytic Streptococcus (2 cases). Susceptibility tests were done to several antibiotics, but the study does not report them. Eighty-five patients responded with favorable results, of which 80 cases were of staphylococcal origin which might have responded to either component alone. The diseases studied are often self-limited. Incision and drainage may frequently be the only treatment needed, an incision and drainage was performed where indicated. There were no controls.

12. *David, N. A., and Day, W. R., Use of a New Tetracycline-Novobiocin Combination in the Treatment of Various Types of Infections. Antibiotic Med. and*

“We don’t have just testimonials. We have a very extensive compilation of studies in vitro, animal, human, coupled with very substantial, very substantial clinical experience, and I think, taking that together, it is a factor.”

Stanley Temko, Upjohn, 8/13/69

14596 RULES AND REGULATIONS

is amended (1) by deleting therefrom the reference to T.D. 69–138 and (2) by adding a reference to this Treasury Decision. As amended the last three lines of the table under this commodity will read:

Country	Commodity	Treasury decision	Action
		69-168	New rate.
		69-190	New rate.
		69-207	New rate.

(R.S. 251, secs. 303, 624, 46 Stat. 687, 759; 19 U.S.C. 66, 1303, 1624)

[SEAL] EDWIN F. RAINS,
Acting Commissioner of Customs.

Approved: September 9, 1969.

EUGENE T. ROSSIDES,
Assistant Secretary of the Treasury.

[F.R. Doc. 69-11240; Filed, Sept. 18, 1969; 8:49 a.m.]

Title 21—FOOD AND DRUGS

Chapter I—Food and Drug Administration, Department of Health, Education, and Welfare

SUBCHAPTER B—FOOD AND FOOD PRODUCTS

PART 19—CHEESES, PROCESSED CHEESES, CHEESE FOODS, CHEESE SPREADS, AND RELATED FOODS

Certain Cheeses, Identity Standards; Confirmation of Effective Date of Order Regarding Use of Additional Safe, Suitable Milk-Clotting Enzymes

In the matter of amending the standards of identity for brick cheese, muenster cheese, edam cheese, limburger cheese, monterey cheese, provolone cheese, caciocavallo siciliano cheese, parmesan cheese, mozzarella cheese, low moisture mozzarella cheese, romano cheese, asiago fresh cheese, hard cheeses, semisoft cheeses, semisoft part-skim cheeses, soft ripened cheeses, spiced cheeses, hard grating cheeses, and skim-milk cheese for manufacturing (21 CFR 19.545, 19.550, 19.555, 19.575, 19.580, 19.590, 19.591, 19.595, 19.600, 19.605, 19.610, 19.615, 19650, 19.655, 19.660, 19,665, 19.670, 19,680, and 19.685) to permit use of all safe and suitable milk-clotting enzymes in cheesemaking:

Pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 401, 701, 52 Stat. 1046, 1055, as amended 70 Stat. 919, 72 Stat. 948; 21 U.S.C. 341, 371) and in accordance with authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120), notice is given that no objections were filed to the order in the above-identified matter published in the FEDERAL REGISTER of June 4, 1969 (34 F.R. 8908). Accordingly, the amendments promulgated by that order became effective August 3, 1969.

Dated: September 12, 1969.

J. K. KIRK,
Associate Commissioner for Compliance.

[F.R. Doc. 69-11176; Filed, Sept. 18, 1969; 8:46 a.m.]

SUBCHAPTER C—DRUGS

PART 130—NEW DRUGS

PART 146—ANTIBIOTIC DRUGS: PROCEDURAL AND INTERPRETATIVE REGULATIONS

Hearing Procedure for Refusal or Withdrawal of Approval of New Drug Applications and for Issuance, Amendment, or Repeal of Antibiotic Drug Regulations; Interpretative Description of Adequate and Well-Controlled Clinical Investigations

The reports of the drug effectiveness review conducted by the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, have resulted and will continue to result in the initiation of formal administrative proceedings to withdraw approval of new drug applications and to repeal regulations which provide for the certification of batches of antibiotic drugs. Before initiating such proceedings, the NAS-NRC reports are published and mailed to interested persons to offer an opportunity to present any available evidence that would satisfy the requirements of law as defined by the term "substantial evidence." If no such evidence is presented, formal proceedings are initiated on the ground there is a lack of substantial evidence to support the effectiveness the drugs purport and are represented to possess.

After the issuance of a notice of opportunity for a hearing on the proposed withdrawal of new drug approval, and after the publication of an order repealing an antibiotic regulation, persons who will be adversely affected are entitled to request a hearing. Before any evidentiary hearing will be ordered, it must appear affirmatively that there is a genuine and substantial issue of fact requiring such a hearing. In the case of novobiocin-tetracycline and novobiocin-sulfamethizole fixed combination drugs, which are the subject of another publication in this issue of the FEDERAL REGISTER, the Commissioner has ruled that the medical documentation offered by the Upjohn Co. in support of its request for a hearing does not provide any adequate and well-controlled clinical investigational data to support the promotional claims, that the agency cannot accept the type of empirical evidence of effectiveness the company seeks to offer through an evidentiary hearing as satisfying the requirement of law for "substantial evidence", and thus that there is no genuine and substantial issue of fact requiring an evidentiary hearing.

The scientific principles which characterize an adequate and well-controlled clinical investigation, and the reasons why the data presented in support of the drug claims do not satisfy these principles, are set forth in that order, and are published here for application in all similar administrative proceedings, whether in connection with the withdrawal of new drug approval or the repeal of antibiotic regulations. Unless a new drug applicant seeking a hearing on the proposed withdrawal of his application or the sponsor of an antibiotic drug covered by a regulation that is being repealed can show a reasonable likelihood that he is prepared to produce "substantial evidence" derived from adequate and well-controlled clinical investigations in support of his promotional claims, there is no basis for a hearing to receive evidence that would not in any event satisfy the legal requirement as to proof of effectiveness.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505, 507, 701(a), 52 Stat. 1052, 1055; 59 Stat. 463; as amended by Public Law 87–781, 76 Stat. 781–782, 785–787, 21 U.S.C. 355, 357, 371(a)) and under authority delegated to the Commissioner (21 CFR 2.120), Parts 130 and 146 are amended as follows:

1. Section 130.12(a)(5) is revised to read as follows:

§ 130.12 Refusal to approve the application.

(a) * * *

(5) (i) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(ii) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is "substantial evidence" to support the claims of effectiveness for "new drugs" and antibiotic drugs.

(a) The plan or protocol for the study must include the following:

(1) A clear statement of the objective of the study.

(2) A method of selection of the subjects that provides for:

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"Three types of controlled comparisons are possible: (i) Placebo control: The new drug entity may be compared quantitatively with an inactive placebo control. This type of study requires at the minimum that the patient not be able to distinguish between the active product and the placebo. Double blinding, to include the clinical observer, may or may not be desirable, depending on the measurement system used to evaluate the results. (ii) Active drug control: The new drug entity may be compared quantitatively with another drug known to be effective in situations where it is not ethical to deprive the subject of therapy. The same considerations to the level of "blinding" apply as with a placebo control study. (iii) Historical control: In some circumstances, involving diseases with high and predictable mortality (acute leukemia of childhood) or with signs and symptoms of predictable duration or severity (fever in certain infections), the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease in comparable patients with not treatment or with treatment with an established effective therapeutic regimen."

JAMA
THE JOURNAL of the American Medical Association
March 4, 1974 Vol 227, No 9

Commentary

This is Medical Progress?

Trends and Consequences of Antibiotic Use in the United States

SINCE the first antibiotic, penicillin G, was marketed in the United States in 1943, these useful and potent antimicrobial agents have been widely adopted and used in the ensuing 30 years. The purpose of this article is to review the trends of antibiotic usage in the United States and try to assess the consequences of the remarkable popularity of this class of drugs.

For editorial comment see p 1048.

While the value and medical usefulness of appropriate antibiotic employment in clinical practice is unquestioned, there has been a considerable controversy over both the type and extent of antibiotic prescribing and the proper indications for use. Furthermore, the ecologic consequences of this wide usage are still unclear. The following are some of the issues:

1. Has the wide use of antibiotics led to the emergence of new resistant bacterial strains?
2. Has the ecology of "natural" or "hospital" bacterial flora been shifted because of antibiotic use?
3. Have nosocomial infections changed in incidence or severity due to antibiotic use?
4. What are the trends of antibiotic use?
5. Are antibiotics properly used in practice?
   - Is there evidence that prophylactic use of antibiotics is harmful and how common is it?
   - Are antibiotics often prescribed without prior bacterial culture?
   - When cultures are taken, is the appropriate antibiotic usually prescribed and correctly used?
   - Why did fixed-dosage antibiotics and chloramphenicol become so popular in spite of many years of warning about their limitations and hazards?
6. Is the increasingly more frequent use of antibiotics presenting the medical community and the public with a new set of hazards that should be approached by some new administrative or educational measures?

With the possible passage of legislation within the next few years that would lead to drug insurance under Medicare, Medicaid, and eventually National Health Insurance, these questions assume a new urgency. How much antibiotic prescribing is desirable and necessary?

Is the public willing to pay for unsubstantiated usages of these drugs or be exposed to the unnecessary risk entailed? In order to help understand these emerging issues, it may be instructive to examine past trends of antibiotic utilization.

Secular Trends of Use of Antibiotics in the United States

There are two sources that permit estimation of total antibiotic utilization in the United States: production and certification figures and marketing research estimates. Production and certification figures can be divided into medicinal and nonmedicinal categories (veterinary use is included in medicinal), but production that is sent to other countries cannot be identified.

With this important deficiency in mind, it is still of interest to examine the production figures for 1960, 1965, and 1970 (Table 2). One can conclude from these figures that production and use of antibiotics for both humans and animals increased rapidly and considerably (over threefold) in the decade between 1960 and 1970, while population increased only 11%.

The Food and Drug Administration must certify all antibiotics produced for human use in the United States. Table 3 illustrates that in 1972, at least 8 billion doses of antibiotics were certified, most of these drugs were for human use in this country. The table also illustrates the striking production figures for the tetracyclines and other surveys have also demonstrated their popularity in medical practice. This finding is somewhat surprising in view of the warnings about using tetracyclines in children and infants (since it can cause mottling of teeth) and the generally accepted superiority of the penicillins for the more common bacterial infections seen in medical practice.

How much of this increased production represents concurrent increased use in human medical practice? Here we must rely on the estimates of marketing research firms. In the period 1964 to 1971, it is estimated that the annual

Reprint requests to the Department of Health, Education, and Welfare, Room 5059-HEW North Building, 330 Independence Ave SW, Washington, DC 20201 (Dr. Simmons).

Table 1.—The Year of First Marketing of Major Antibiotics in the United States*

1948	Penicillin G
1947	Streptomycin
1948	Chlortetracycline
1949	Chloramphenicol
1950	Oxytetracycline
1951	Polymyxin B
1952	Erythromycin
1953	Tetracycline
1954	Nystatin
1955	Penicillin V
1957	Amphotericin B
1958	Vancomycin
1959	Phenethicillin, Rolitetracycline, Demeclotetracycline
1960	Methicillin
1961	Colistin
1962	Kanamycin, Oxacillin
1963	Ampicillin
1964	Cephalothin
1965	Cloxacillin
1966	Gentamicin
1967	Doxycycline
1968	Dicloxacillin, Cephaloridine
1970	Carbenicillin, Clindamycin
1971	Cephalexin, Rifampin, Capreomycin
1972	Spectinomycin

*Provided by the Food and Drug Administration.

Table 2.—Annual Production of Antibiotics in the United States*

	Year		
	1960	1965	1970
Medicinal	3.0	4.7	9.5
Feed-additive	1.2	2.6	7.3
Total	9.6	7.3	16.9

*Production is in millions of pounds.

Table 3.—Antibiotic Certification by Food and Drug Administration, 1972*

Rank Order, Name	In Millions of Grams Certified
1, Tetracyclines	822
2, Penicillins	400
3, Erythromycins	302
4, Ampicillins	271
5, Cephalosporins	70
6, Semisynthetics	21
7, Chloramphenicol	8

*Provided by the Food and Drug Administration.

Fig 1.—Number of new and refilled prescriptions of antibiotics. (Provided by Lea, Inc, Ambler, Pa.)

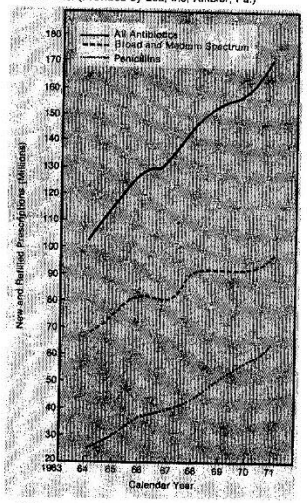
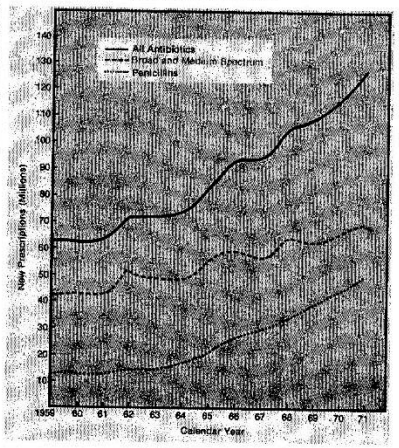


Fig 2.—Number of new prescriptions of antibiotics.



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the rational and irrational use of systemic antimicrobial drugs

by ANDREW W. ROBERTS and JAMES A. VISCONTI

► THE EXTENSIVE USE OF SYSTEMIC ANTIMICROBIALS in hospitalized patients as reported in the last ten years has been a topic of concern to many investigators.[1-10] Much of this concern originated from the observation that many physicians do not seem to recognize the hazards of the indiscriminate use of antimicrobial drugs and often prescribe antimicrobials prophylactically for what might be termed "security" in treatment.[11-13] The concept that if one antimicrobial is good, two should be better and three will cure virtually anybody of anything has long been refuted, although it is still being employed.[14-16]

Repeated observations of misuse and overuse of prescription drugs at the same time have led to a growing interest of society in the need for drug utilization review programs.[15-24] This emphasis has been particularly strong in the area of the relatively expensive antimicrobials since studies have indicated that approximately one-third of all hospitalized patients on any given day receive some type of systemic antimicrobial.[2-4,8,9]

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Presented at the 29th Annual Meeting of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, Houston, Texas, April 25, 1972.

In an attempt to better define the extent of antimicrobial use, a study was conducted to indicate antimicrobial usage patterns in an institutional setting. Prevalence and trends of use, indications for that use, antimicrobial usage patterns, appropriateness of antimicrobial therapy, incidence of adverse reactions and cost factors were studied and evaluated.

This study, hopefully, will serve to formulate a practical design for further continuing community studies of antimicrobial utilization. This will make it possible to develop a framework for studying corrective programs including the pharmacist's role and the appropriate level of health expenditures for a program of improving antimicrobial therapy.

Methods

All patients admitted to a 500-bed, nongovernmental community hospital during a one-month period, excluding the newborn and those patients admitted directly to the labor room, intensive care or coronary care units, were monitored by pharmacists throughout their hospital stay for the administration of antimicrobial agents. Antimicrobials not included were topical and nonabsorbable agents. Table 1 lists the drugs monitored in the study. As patients received antimicrobial therapy, their history was carefully reviewed and personal characteristics were recorded together with all pertinent diagnoses, clinical data, preadmission medication (e.g., antibiotics, steroids, cancer chemotherapeutic agents) and results of laboratory examinations on a standardized data collecting form. Thereafter, detailed and standardized records were maintained describing the patient's clinical course; antimicrobial agents administered and their dose, fre-

American Journal of Hospital Pharmacy 29 (1972): 828-34

Image from the University of Arizona

Calvin Kunin

on the medical profession and the pharmaceutical industry. This would only be ignoring a deeper set of problems. It would be a grave mistake to assign fault without understanding the pathogenesis of the problem. We are dealing with a multifactorial phenomenon that requires an assessment of the constraints of practice. These include the difficulties of making an etiologic diagnosis of infectious disease, the weakness and lack of integration of clinical microbiology services, and the inadequacy of training of students and housestaff in clinical infectious disease. Added to this is the excessive expectation of the efficacy of antimicrobial therapy by both patients and physicians and the ready solution to these problems offered by a confusing variety of well-advertised, readily available drugs.

We know that complex problems are not solved by "declaring war" on them. The lessons of the "wars" on poverty, cancer, heart disease, and stroke and the wasteful support of large-scale disease-oriented categorical programs are fresh in our minds. It is now apparent that perhaps too much was expected of PSROs (3) and the same may be true for HMOs as well. Nor will we profit by making scapegoats of the medical schools. Legislating curriculum changes, or placing our bet on postgraduate education, or producing a new breed of clinical pharmacists may not be the right answers. We can proceed better by developing a firm base of knowledge about the nature of the problem and working out proven and cost-effective strategies rather than by plunging ahead in dubious battle. We must first show that our efforts will be both safe and effective.

Some examples in the antibiotic field may help to explain these words of caution. A decade ago some of us working in this field believed that we had scored a major victory when the Food and Drug Administration removed fixed-dose combination antibiotics from the market. These included irrational combinations of penicillin, streptomycin, tetracycline, and novobiocin. This was no victory, but abject defeat; these drugs were almost immediately replaced by the more expensive parenteral cephalosporins for surgical prophylaxis and the oral cephalosporins, new tetracyclines, and clindamycin in office practice. Chloramphenicol may not be often used by the prudent physician, but other drugs such as long-acting expensive tetracyclines and ampicillin and amoxacillin have taken its place. I do not mean to imply that removing irrational drugs was a mistake in itself, but we expected too much for our efforts.

An industry has developed in the past few years for surveillance and prevention of hospital-acquired infection and, more recently, for control of antibiotic use. The Joint Commission on Accreditation of Hospitals (JCAH) now requires committees, infection control nurses, pharmacists, and clinicians to be engaged in what appears to be enormous amounts of busywork. Valuable time is spent writing replicative procedure manuals to satisfy inspectors who are often not aware of what they really want or need. Our own infection-control nurse spends much of her time preparing for the next inspection rather than working on the wards where she belongs. Should we raise hospital costs further by hiring a clinical pharmacist to monitor antibiotic use as well? All of this is premature until we can prove that each effort will be effective in the medical care system.

This is a good time to look at the impact of infectious disease in the United States and consider priorities for future research. Hence a committee representing a wide range of disciplines engaged in patient care in infectious disease (medicine, surgery, obstetrics-gynecology, hospital infection control, clinical microbiology, antimicrobial therapy, administration, and government) was asked by Drs. Richard Krause and William Jordan of the NIAID to bring together people engaged with these problems for a 2-day symposium at the National Institutes of Health (NIH) on 30-31 May 1978. The NIAID, with its mission to make its research efforts more relevant to the needs of medical practice, has established a branch on clinical studies headed by Dr. Robert Edelman.

The issues raised in the symposium included the frequency of infections and their impact on human welfare and economic costs; experiences with infectious diseases in community practice as well as in tertiary care facilities; practical problems of hospital-acquired infections and the clinical microbiology laboratory; and patterns of use of antibiotics and manpower needs in the disciplines relevant to control of infectious disease. To place the issues in context, public policy considerations of regulations, standards, or practice, and the relation of the drug industry to medical practice were explored. Finally a group of well-qualified people looked at illnesses that appear most critically important in the near future.

I hope that the data and views presented in this symposium, published as a supplement (Part 2) to this issue, will provide the NIAID with a guide to plan for support of research and training in clinically relevant areas of infectious disease. Rather than declaration of war on anything, each proposed area of research or tactic should be subjected to the high standards set for any worthy investigation. Not all of the problems considered are within the scope of the NIH mission. We must not expect that some magical surge of money will resolve these problems. Perhaps most will be gained by a better understanding of the issues and how we might proceed. (CALVIN M. KUNIN, M.D., F.A.C.P.; *Department of Medicine, University of Wisconsin, and the Medical Service of the William S. Middleton Veterans Administration Hospital; Madison, Wisconsin*)

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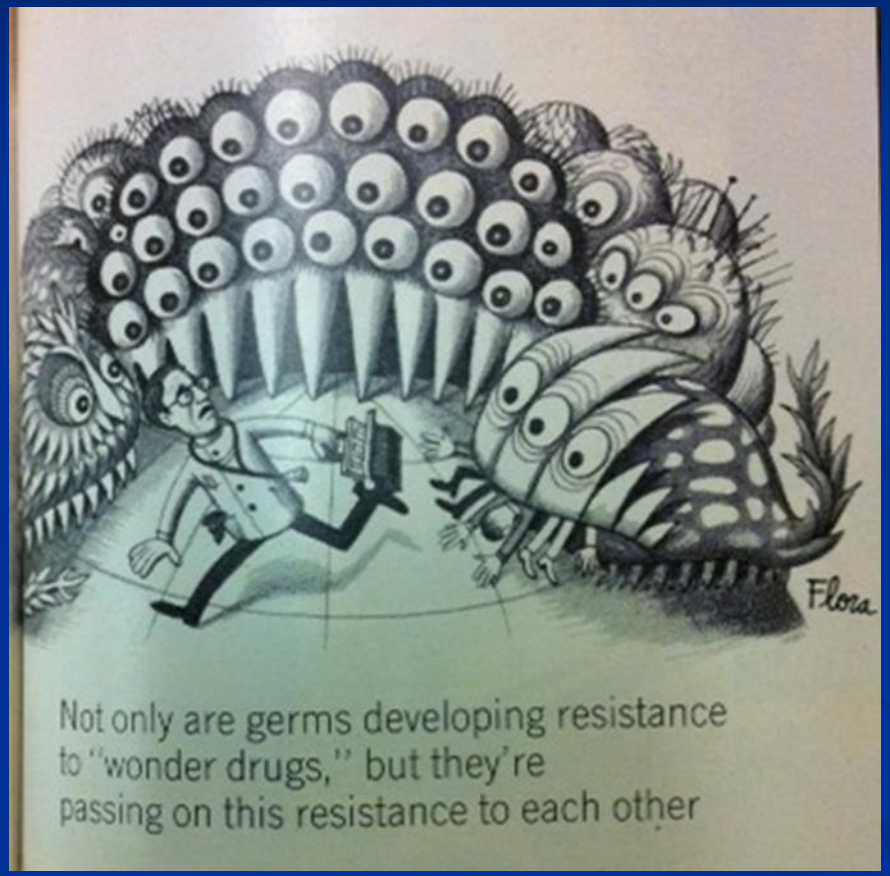
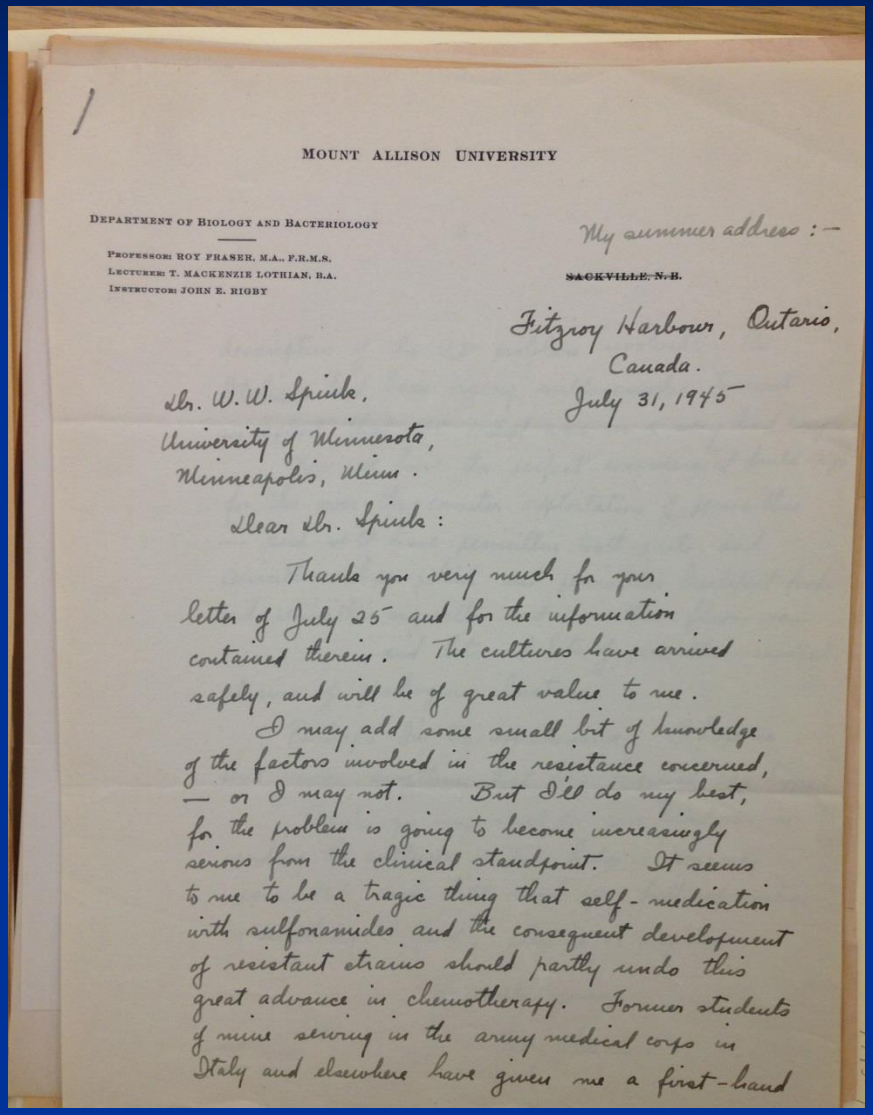
Annals of Internal Medicine 89 Part 1 (1978): 716-717

III. Confronting the "Superbug"



First era, 1940s-1963



MOUNT ALLISON UNIVERSITY

DEPARTMENT OF BIOLOGY AND BACTERIOLOGY

PROFESSOR: ROY FRASER, M.A., F.R.M.S.
LECTURER: T. MACKENZIE LOTHIAN, B.A.
INSTRUCTOR: JOHN E. RIGBY

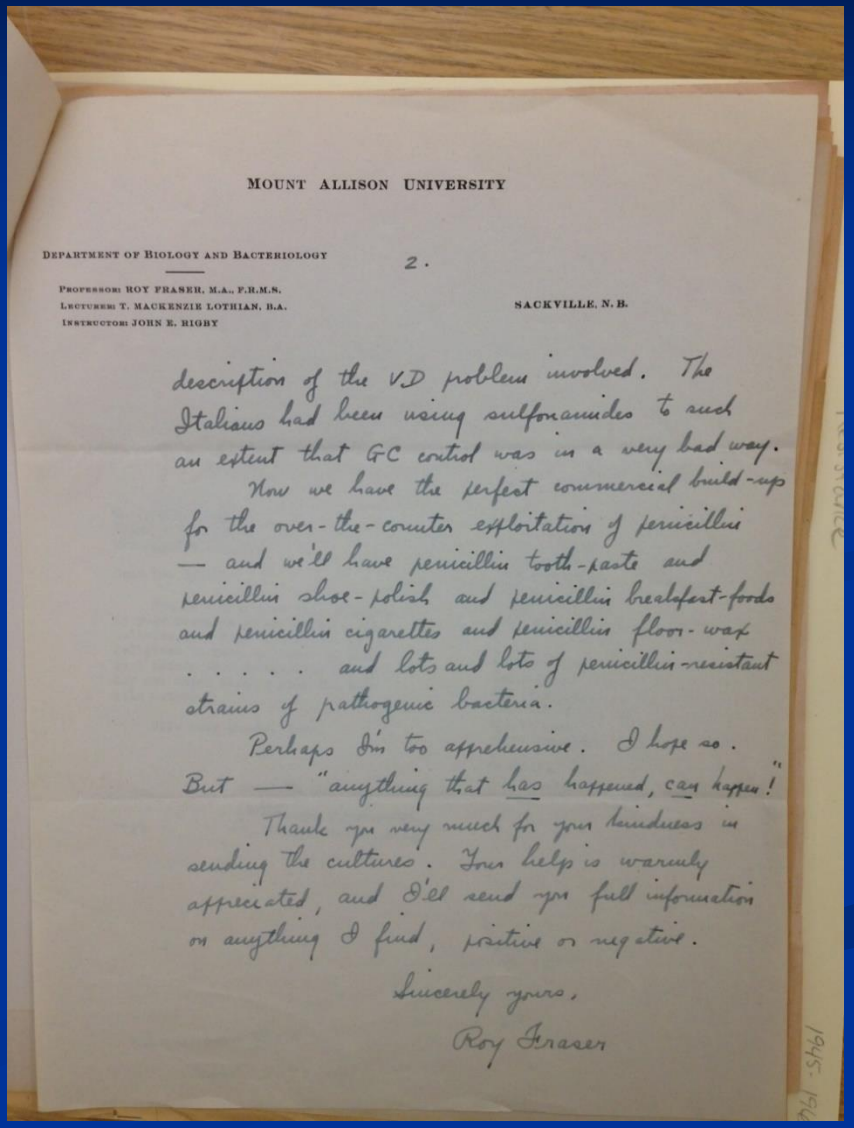
My summer address :—
~~SACKVILLE, N.B.~~
Fitzroy Harbour, Ontario,
Canada.
July 31, 1945

Dr. W. W. Spink,
University of Minnesota,
Minneapolis, Minn.

Dear Dr. Spink:

Thank you very much for your letter of July 25 and for the information contained therein. The cultures have arrived safely, and will be of great value to me.

I may add some small bit of knowledge of the factors involved in the resistance concerned, — or I may not. But I'll do my best, for the problem is going to become increasingly serious from the clinical standpoint. It seems to me to be a tragic thing that self-medication with sulfonamides and the consequent development of resistant strains should partly undo this great advance in chemotherapy. Former students of mine serving in the army medical corps in Italy and elsewhere have given me a first-hand



MOUNT ALLISON UNIVERSITY

DEPARTMENT OF BIOLOGY AND BACTERIOLOGY

2.

PROFESSOR: ROY FRASER, M.A., F.R.M.S.
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INSTRUCTOR: JOHN E. RIGBY

SACKVILLE, N. B.

description of the VD problem involved. The Italians had been using sulfonamides to such an extent that GC control was in a very bad way.

Now we have the perfect commercial build-up for the over-the-counter exploitation of penicillin — and we'll have penicillin tooth-paste and penicillin shoe-polish and penicillin breakfast-foods and penicillin cigarettes and penicillin floor-wax . . . . . and lots and lots of penicillin-resistant strains of pathogenic bacteria.

Perhaps I'm too apprehensive. I hope so. But — "anything that has happened, can happen!"

Thanks you very much for your kindness in sending the cultures. Your help is warmly appreciated, and I'll send you full information on anything I find, positive or negative.

Sincerely yours,
Roy Fraser

Wesley Spink papers, University of Minnesota

JOINT MEETING No. 1

Section of General Practice with Section of Medicine

Chairman—R. J. MINNITT, M.D., F.F.A. R.C.S., F.R.C.O.G.
(President of the Section of General Practice)

[*November* 24, 1954]

DISCUSSION ON THE USE AND ABUSE OF ANTIBIOTICS

Dr. David Wheatley: *Uses of Antibiotics*

Until recently, as far as the general practitioner was concerned, antibiotics could be divided into two groups, those which were freely prescribable and those which could only be obtained through the hospital service. In the first group are penicillin, streptomycin, chloramphenicol, erythromycin and the sulphonamides, for the last-mentioned are no less an antibiotic than the others and must be considered in conjunction with them. In the second group are the tetracyclines (Aureomycin, Terramycin and tetracycline itself), the polymyxins and a heterogeneous medley tailing off in practical usefulness. Erythromycin may be dismissed immediately except for the rare case of infection resistant to all the other antibiotics. When indicated, at the present time it is probably better to use an antibiotic from the second group in preference to erythromycin, because of the latter's strong capacity for inducing drug resistance. However, as in the case of penicillin, time may show this to be a false fear as far as general practice is concerned, but it must be remembered that erythromycin covers only the same bacterial spectrum as penicillin itself. Likewise there will be little indication to use streptomycin alone because of its ototoxicity, although the risk of the latter may be reduced by using a streptomycin-dihydrostreptomycin mixture. I am not including the treatment of tuberculosis as this is usually undertaken by the chest clinics. This leaves penicillin, the sulphonamides and chloramphenicol which have been our mainstay in general practice, until the recent release of the newer antibiotics.

Sometimes it may be expedient to combine two antibiotics, and here it should be remembered that antibiotics may be divided, roughly, into two groups. The first includes penicillin, the sulphonamides and streptomycin, all of which are synergistic with each other. The second group includes chloramphenicol, Aureomycin, Terramycin, &c., these also being synergistic one with the other. Members of one group, however, are antagonistic to members of the other and should not be combined.

As bacteriological examination may often be delayed, some reliance must be placed upon "blind" therapy. Table I shows some of the commoner bacteria with their degrees of sensitivity to different antibiotics.

TABLE I.—BACTERIAL SENSITIVITIES

	Sulphonamides	Penicillin	Streptomycin	Chloramphenicol	Aureomycin	Terramycin
Staph. aureus	+	++++	++	++	++	++
Str. hæmolyticus	+++	++++	−	++	+++	++
Pneumococcus	+++	++++	++	+++	+++	++
H. pertussis	−	−	−	++	?+	?+
Bact. coli	+++	−	+++	+++	++	+++
Bact. sonnei	+++	−	+	+++	++	+++
Neisseria	+++	++++	−	++	++	++
Proteus	−	−	+	+	−	?
Pseudomonas	−	−	?+	?+	?+	?

We are now in a position to decide which antibiotic or combination of antibiotics is most suitable for each infection and Table II shows some of the commoner conditions met with in general practice. In each case the antibiotic of choice is shown, together with the next most suitable one. If there is no response within thirty-six hours, the second choice should be substituted, or whatever other antibiotic may be indicated as a result of bacteriological examination and sensitivity tests.

Mode of administration.—Frequent injections are clearly impossible in general practice, therefore in the case of penicillin, reliance must be placed upon twelve- or twenty-four-hourly injections, or upon oral therapy. Hence we have here a major difference between domiciliary and hospital practice, as the widespread use of oral penicillin is almost entirely confined to general practice. Hence the general practitioner is in a more favourable position to form an opinion as to its effectiveness.

Three of the more common conditions are (1) Minor Pyogenic; (2) Acute Tonsillitis and Pharyngitis; (3) Acute Otitis Media.

sensitizing. The "penicillin umbrella" should be reserved for real impending storms and not unfurled and hoisted at every threatened shower.

Wastage.—Some may say that wasting is merely an economic sin. I cannot agree.

Economy—the nice adjustment of means to ends—pertains, I am sure, to the *καλὸν κ'ἀγαθὸν*—the beautiful and good. Waste, its opposite, pertains to the *αἰσχρόν και κακόν*—the ugly and bad. I can adduce no evidence that antibiotics *are* wasted.

The Medical Research Council (1954) published the results of a trial of systemic antibiotics in certain dermatoses. The substances included Aureomycin, chloramphenicol and Terramycin and they proved useless for herpes simplex recurrens, dermatitis herpetiformis, pityriasis rosea, lichen planus, discoid eczema and plantar warts. I cannot believe the M.R.C. would have conducted this research had not many practitioners thought these might possibly be of benefit. Chloramphenicol has no effect on whooping cough after the first week and it has no very startling effect even then. Its occasional use may be justifiable but I feel myself that even if it could not cause aplastic anæmia the use as a palliative of so very costly a remedy in an illness often no worse than a nuisance comes perilously near to abuse.

Then there is oral penicillin. Anyone who dislikes stabbing children must want to believe in its efficacy but the finding of Fairbrother and Daber (1954) last April that "absorption was irregular irrespective of the nature of the compound and the age of the recipient" rings true to me and I cannot help thinking it is abuse on the score of waste and futility to give it as a first dose in acute infection and doubtful practice to give it to adults at all.

Penicillin lozenges I think may constitute an abuse by merely existing.

The third, most subtle and, in the long run, probably worst abuse is queering the pitch for our successors—or even for ourselves if we go on playing. Those deadly staphylococci, those monilia in permanent possession of the field are not pirates or privateers accidentally encountered, they are detachments of an army. They are also portents.

We were scoffed at long since for "pouring medicines of which we know little into bodies of which we know less". Browne (1954), reporting the moniliasis, remarks: "one of the risks of using antibiotics is that their selective action may disturb the bacterial equilibrium of the gut or lung".

There are parallels in agriculture.

We plough the fields and scatter insecticides and selective weed-killers on the land and we find we have killed birds, bees and flowers who minister in various ways to our health and happiness and with whom we have no quarrel. With a little more knowledge I am sure I could tell you of pests we have unwittingly encouraged. We should study the balance of Nature in field and hedgerow, nose, throat and gut before we seriously disturb it.

Again, we may come to the end of antibiotics. We may run clean out of effective ammunition and *then* how the bacteria and moulds will lord it.

A leader-writer quotes the Mayo Clinic who "wish to emphasize that they do not advocate the use of erythromycin in chronic infections such as osteomyelitis, bacterial endocarditis, &c., because of the strong likelihood of provoking bacterial resistance. They *abhor its indiscriminate use*" (*see Brit. med. J.*, 1954).

"*ὁ βίος βραχὺς, ἡ δὲ τέχνη μάκρα*" "Life is short but the Art is long."

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Dr. J. D. N. Nabarro: The abuses of antibiotics may be considered under two headings, using them unnecessarily and using them unwisely.

Antibiotics may be regarded as being used unnecessarily when they are given by injection, by mouth, or used as a local application in cases of minor or self-limiting conditions from which a good recovery may be expected without their use. If the antibiotics were completely innocuous drugs with a potentiality only for doing good, the sole objection to their use in minor illnesses would be their cost—admittedly an important consideration in some instances. In fact, however, this is far from the case. There are at least four ways in which the unnecessary use of antibiotics may be harmful to the individual patient, or to the population in general. It may harm the patient by giving rise to undesirable side-effects, it may harm him by interfering with the development of antibodies and it may harm him by sensitizing

Proceedings of the Royal Society of Medicine 48 (1954): 355-364

A Proposed Crusade for the Rational Use of Antibiotics

ALLEN E. HUSSAR

Franklin Delano Roosevelt Veterans Administration Hospital, Montrose, New York

Good fortune and well organized research of the past 13 years have produced highly effective therapeutic agents to combat infections. There are at least 12 antibiotics now available to the physician with which to successfully curtail human suffering and substantially diminish mortality. Antibiotic research marches on toward three goals: (1) to find new and better agents, (2) to produce better preparations of the presently known drugs, and (3) to find more effective and less harmful methods of antibiotic administration. The extent of these efforts is best illustrated by the wealth of material presented during the Antibiotic Symposium.

Unfortunately, the clinical practice of antibiotic therapy has shown a strong tendency to disregard the admirable results of antibiotic research. Today, a large proportion of the antibiotics are unnecessarily or incorrectly administered. It is hardly necessary to prove to this audience the validity of this statement.

Correction of this adverse situation would advance the efficacy of antibiotic therapeusis just as far, or, perhaps even farther than would the discovery of another broad-spectrum antibiotic, or the introduction of an additional repository penicillin preparation. Therefore, this situation deserves the attention of this Antibiotic Symposium and calls for a serious attempt to find an effective remedy for the problem.

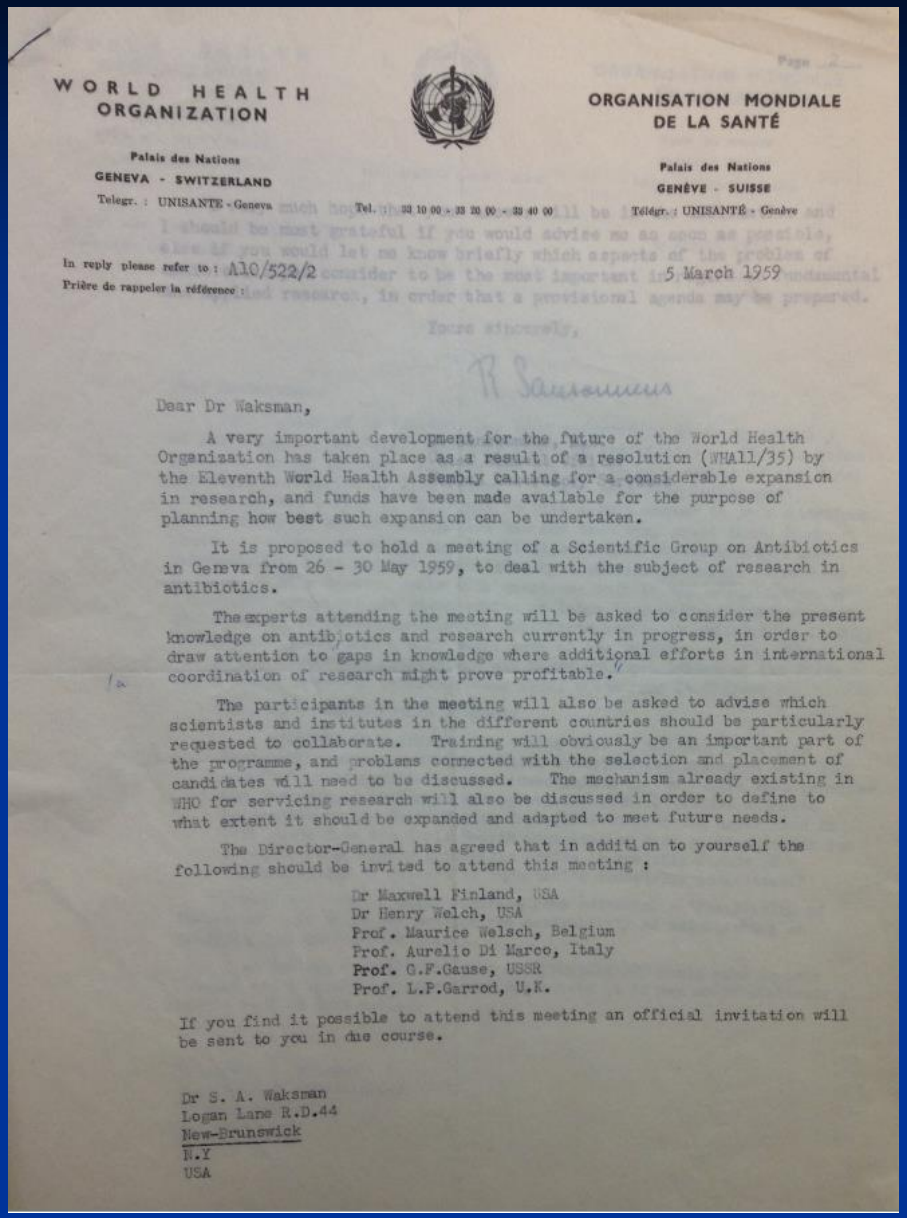
THE INDISCRIMINATE USE OF ANTIBIOTICS

No doubt, the indiscriminate prescription of antibiotics is practiced on a much larger scale outside rather than inside of hospitals. The administration of an antibiotic just because the patient complains of a "cold," pain in the chest, diarrhea, urinary frequency, or elevated temperature is a common office and home practice. One rarely sees a patient referred to a clinic or hospital who has not already received some antibiotic medication. Antibiotics are ordered by telephone for the patient who calls his doctor, complaining of fever or cough. We are forced to do bacteriologic studies on patients who were given "a shot of penicillin" for the trip to the hospital. And this story could be continued indefinitely.

An analysis by this speaker of the case reports of fatal antibiotic reactions has revealed that about one half of these unfortunate patients died from unnecessary medication.

In order to find out to what extent antibiotics are used in hospital wards today, a survey was made of the general medical services of five prominent metropolitan hospitals (table I). Of the total of 1,109 medical patients, 353, or 32 per cent, had received antibiotics at some time after admission. As the table shows, this figure varied from 25 to 41 per cent with the different hospitals. In hospitals A and C, where strict indications had been set up for the administration of antibiotics, the percentages were 26 and 25, respectively. These two figures are also almost identical with the 23 per

Antibiotics Annual (1954-1955): 379-382



WORLD HEALTH ORGANIZATION

Palais des Nations
GENEVA - SWITZERLAND
Telegr. : UNISANTE - Geneva
Tel. : 33 10 00 - 33 20 00 - 33 40 00

ORGANISATION MONDIALE DE LA SANTÉ

Palais des Nations
GENÈVE - SUISSE
Télégr. : UNISANTÉ - Genève

In reply please refer to : A10/522/2
Prière de rappeler la référence :

5 March 1959

Dear Dr Waksman,

A very important development for the future of the World Health Organization has taken place as a result of a resolution (WHA11/35) by the Eleventh World Health Assembly calling for a considerable expansion in research, and funds have been made available for the purpose of planning how best such expansion can be undertaken.

It is proposed to hold a meeting of a Scientific Group on Antibiotics in Geneva from 26 - 30 May 1959, to deal with the subject of research in antibiotics.

The experts attending the meeting will be asked to consider the present knowledge on antibiotics and research currently in progress, in order to draw attention to gaps in knowledge where additional efforts in international coordination of research might prove profitable.

The participants in the meeting will also be asked to advise which scientists and institutes in the different countries should be particularly requested to collaborate. Training will obviously be an important part of the programme, and problems connected with the selection and placement of candidates will need to be discussed. The mechanism already existing in WHO for servicing research will also be discussed in order to define to what extent it should be expanded and adapted to meet future needs.

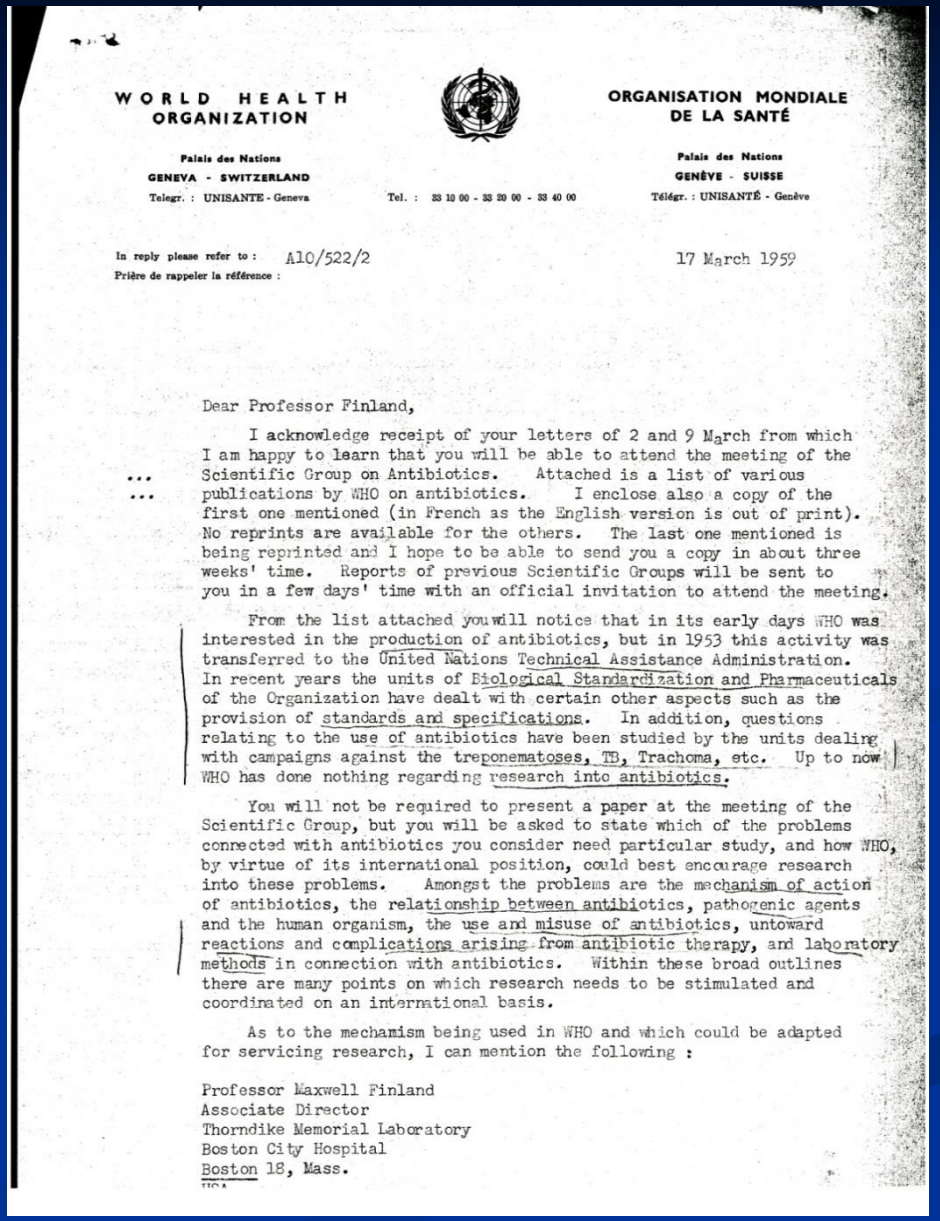
The Director-General has agreed that in addition to yourself the following should be invited to attend this meeting :

Dr Maxwell Finland, USA
Dr Henry Welch, USA
Prof. Maurice Welsch, Belgium
Prof. Aurelio Di Marco, Italy
Prof. G.F.Gause, USSR
Prof. L.P.Garrod, U.K.

If you find it possible to attend this meeting an official invitation will be sent to you in due course.

Dr S. A. Waksman
Logan Lane R.D.44
New-Brunswick
N.Y
USA

Selman Waksman Papers, Rutgers University



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ORGANISATION MONDIALE DE LA SANTÉ

Palais des Nations
GENÈVE - SUISSE
Télégr. : UNISANTÉ - Genève

In reply please refer to : A10/522/2
Prière de rappeler la référence :

17 March 1959

Dear Professor Finland,

I acknowledge receipt of your letters of 2 and 9 March from which I am happy to learn that you will be able to attend the meeting of the Scientific Group on Antibiotics. Attached is a list of various publications by WHO on antibiotics. I enclose also a copy of the first one mentioned (in French as the English version is out of print). No reprints are available for the others. The last one mentioned is being reprinted and I hope to be able to send you a copy in about three weeks' time. Reports of previous Scientific Groups will be sent to you in a few days' time with an official invitation to attend the meeting.

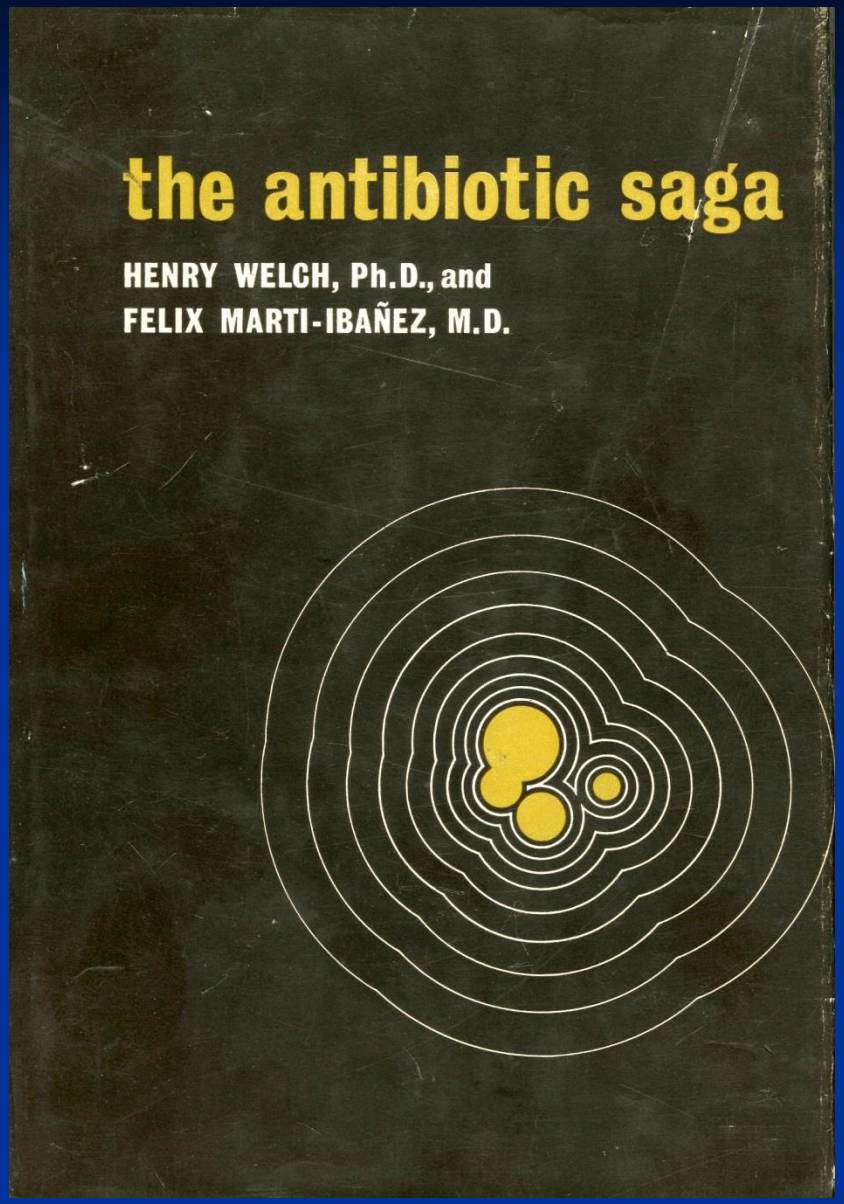
From the list attached you will notice that in its early days WHO was interested in the production of antibiotics, but in 1953 this activity was transferred to the United Nations Technical Assistance Administration. In recent years the units of Biological Standardization and Pharmaceuticals of the Organization have dealt with certain other aspects such as the provision of standards and specifications. In addition, questions relating to the use of antibiotics have been studied by the units dealing with campaigns against the treponematoses, TB, Trachoma, etc. Up to now WHO has done nothing regarding research into antibiotics.

You will not be required to present a paper at the meeting of the Scientific Group, but you will be asked to state which of the problems connected with antibiotics you consider need particular study, and how WHO, by virtue of its international position, could best encourage research into these problems. Amongst the problems are the mechanism of action of antibiotics, the relationship between antibiotics, pathogenic agents and the human organism, the use and misuse of antibiotics, untoward reactions and complications arising from antibiotic therapy, and laboratory methods in connection with antibiotics. Within these broad outlines there are many points on which research needs to be stimulated and coordinated on an international basis.

As to the mechamism being used in WHO and which could be adapted for servicing research, I can mention the following :

Professor Maxwell Finland
Associate Director
Thorndike Memorial Laboratory
Boston City Hospital
Boston 18, Mass.
USA

Maxwell Finland Papers, Countway Medical Library



have extended life and lowered the death rate, we still do not have a definitive cure for this dreaded disease. In all these areas of medicine and in others there are infinite opportunities for improvement, and against all of these diseases an army of investigators is constantly seeking the answers. In the fight against cancer alone, millions of dollars are being spent yearly in an attempt to find a cure. Although we are nowhere near the end, progress is rapid and certain and the time will come, and within this century, when we will be looking for a disease for a newly discovered drug to cure! In the meantime physicians will continue everyday in hospitals and offices, at the patient's bedside, and in the midst of epidemics writing, with their endeavors and ideas, new and luminous chapters of the Antibiotic Saga.

The Antibiotic Saga (New York: Medical Encyclopedia, Inc., 1960)

MEDICAL PROGRESS

EMERGENCE OF ANTIBIOTIC-RESISTANT BACTERIA (Concluded)*

MAXWELL FINLAND, M.D.†

BOSTON

BIOLOGIC AND BIOCHEMICAL PROPERTIES OF ANTIBIOTIC-RESISTANT STRAINS

Comparisons of Sensitive and Resistant Strains of the Same Species

Although the mechanisms involved in the development of antibiotic resistance will not be considered in detail, some studies designed to elucidate the problem and some illustrations of differences between sensitive and resistant strains may be mentioned. Bellamy and Klimek[473] noted that a penicillin-resistant variant of *Staph. aureus* grew more slowly than its sensitive parent culture and also lost its ability to grow anaerobically. They could not increase significantly the resistance of strains of *Str. faecalis*, *Str. mastitidis* or *Clostridium welchii* by similar methods. They suggested that organisms that depend on anaerobic processes for their energy supply will not become appreciably resistant to penicillin. Changes in metabolic activities and growth requirements of streptomycin-resistant organisms have also been reported by many workers,[474-477] but streptomycin-inactivating substances could not be demonstrated in such organisms or their products.[476] Anderson[478] pointed out a number of metabolic and biochemical changes in a strain of staphylococcus isolated from a patient and found to be resistant to 5 antibiotics; some of these changes had also been described in strains made highly resistant in vitro. Alexander and Leidy[479] induced streptomycin resistance in *H. influenzae* by exposing sensitive strains to extracts of resistant ones; this was shown to be associated with transfer of desoxyribonucleic acid (DNA) from the resistant strain in the same manner that Hotchkiss produced penicillin-resistant strains of pneumococci[480] and other streptomycin-resistant organisms.[481] Without consideration of the details of the genetic aspects,[6,7,9] it is now recognized that most organisms acquire resistance stepwise by grades that vary for different antibiotics and different species. However, high degrees of resistance to streptomycin — and also to isoniazid and occasionally other agents — may emerge suddenly in a single stage. Kaipainen,[482] for example, demonstrated completely penicillin-resistant variants of 2 originally sensitive strains of *Bacillus subtilis* after a single cultivation in broth containing penicillin. Both the stepwise and the single large-step types of resistance have been observed to develop simultaneously by several workers.[287,483,484]

Beljanski,[485,486] comparing streptomycin-resistant and streptomycin-sensitive variants of the same strains of *Staph. aureus* and *Esch. coli*, found that the latent phase of growth of the resistant strains was more prolonged than in the corresponding sensitive strains and they accumulated more ribonucleic acid, and only this substance, at the end of the latent phase. Other constituents showed no difference; these included proteins, orthophosphates, ribose and desoxyribose nucleotides and desoxyribonucleic acid. A penicillin-resistant variant of the same strain of *Staph. aureus* accumulated not only ribonucleic acid but also proteins, purine nucleotides and phosphorolated acid-soluble compounds. Penicillin was considered not to interfere with depolymerization of ribonucleic acid, which degrades and then participates in protein synthesis. Streptomycin, on the other hand, combines with ribonucleic acid (or with nucleoproteins) and prevents its depolymerization. A sulfonamide-resistant *Staph. aureus* exhibited a prolonged latent period during which it accumulated twice as much desoxyribonucleic acid as its sensitive parent; this was in contrast to the streptomycin-resistant and penicillin-resistant variants, which accumulated more ribonucleic acid and not desoxyribonucleic acid. Streptomycin-resistant strains of *S. enteritidis*[486] behaved differently from the other species; they were richer in desoxyribonucleic acid than their sensitive parents. Rates of multiplication of the resistant variants did not depend on the amounts of ribonucleic acid.

Hobson[487] could establish no change in the properties of erythromycin-resistant strains as compared with their parent erythromycin-sensitive strains, except slower growth and crossresistance to carbomycin.

Eagle,[488] using isotopically labeled penicillin, demonstrated that, in addition to extracellular penicillinase production, by which bacteria convert penicillin to penicilloic acid, or, as in 1 instance, dependence on penicillin for multiplication, there are at least 3 mechanisms of penicillin resistance: a number of strains degrade penicillin after it enters the cell — this was found in *Esch. coli, P. morganii* and *Shigella paradysenteriae;* the resistant strains bind less penicillin than the sensitive ones; and, by some unknown mechanism, cells of penicillin-resistant variants of normally sensitive strains may combine with penicillin to the same degree as the cells of the parent sensitive strains without being killed.

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

Work cited from this laboratory was aided by a grant from the United States Public Health Service.

Portions of this paper were prepared for and presented at the International Conference on the Use of Antibiotics in Agriculture, organized by the National Academy of Sciences—National Research Council through the Agricultural Research Institute of the Division of Biology and Agriculture, Washington, D. C., October 21, 1955.

†Associate professor of medicine, Harvard Medical School; chief, Fourth Medical Service, Boston City Hospital; associate director, Thorndike Memorial Laboratory, Boston City Hospital.

COMPLICATIONS INDUCED BY ANTIMICROBIAL AGENTS*

MAXWELL FINLAND, M.D.,† AND LOUIS WEINSTEIN, M.D.‡

BOSTON

THE widespread use of antimicrobial agents may have completely resolved many perplexing problems in the field of infectious diseases but it has also created many new and even more perplexing ones. Among these are the various untoward effects, which have been increasing steadily; some are directly toxic, some are allergic, and others are related to the biologic activities of the chemotherapeutic substances. The reasons for an increased prevalence of undesirable sequelae to chemotherapy are mainly three: the increase in the number of antimicrobial agents, each of which may produce such reactions; the increase in the number of people treated so that, even had the incidence remained constant, the total number of reactions would have risen; and repeated administration of single or multiple agents so that ever-increasing numbers of people are conditioned to show various manifestations of hypersensitivity when exposed to these drugs.

The list of the undesirable effects actually observed and attributed to therapy with the widely used antimicrobial agents is long and varied and involves most of the organ systems. Not all the complications have occurred with each of the chemotherapeutic substances, and some have been noted with only one or another of them. Moreover, the incidence of the individual reactions varies widely both among the different agents and for any one of them. Only some of the salient features of these side effects can be touched upon in this brief presentation; for convenience they are discussed in relation to the different organ systems involved.

CUTANEOUS MANIFESTATIONS

The most common untoward reactions to systemic administration of antimicrobial agents are manifested in the skin by a large variety of lesions; most of them are probably a result of sensitization and are frequently accompanied by fever and pruritus. These lesions may occur either during therapy or soon after the administration of the same or a related agent is resumed. They may be transient, but most often they increase in intensity and change their character, or are followed by more serious consequences if the treatment is continued after the eruptions appear.

The cutaneous lesion most frequently seen with all the agents is a morbilliform eruption; less frequent are the scarlatiniform, urticarial, vesicular or bullous eruptions, which may be very incapacitating. Purpuric lesions, with or without thrombocytopenia, may also occur; although some of these are merely superficial or perhaps manifestations of serum-sickness-like reactions, blood vessels may be involved, occasionally giving rise to extensive, severe necrosis of large areas of skin. Skin lesions may also resemble the various forms described under the term erythema multiforme. Some agents, notably sulfathiazole, produce the typical lesions and distribution of erythema nodosum accompanied by conjunctival injection and episcleritis. The most severe manifestation in the skin, however, is exfoliative dermatitis, which may follow the morbilliform or scarlatiniform lesions when the offending agent is not removed; it may be extremely incapacitating and is sometimes fatal.

Local inflammatory reactions may occur at the sites of injections; they vary in frequency with different agents and sometimes with various lots of preparations of the same agent. They may be due to the specific irritating character of the broad-spectrum antibiotic injected or to the hypertonicity of the solutions, as when large doses of penicillin and streptomycin are given in small volumes of fluid. Sometimes the high concentration of cations or anions of these two drugs respectively may be the cause.

In the management of the skin lesions the most important measure is the discontinuance of the drugs and promotion of their elimination. The antihistaminic drugs may be helpful, particularly in combating the pruritus, and occasionally they reduce the severity of lesions or limit their spread. ACTH and cortisone may be of benefit and are sometimes even life saving in cases of exfoliative dermatitis or in patients with severe and extensive urticarial or bullous eruptions. These hormones also relieve the pruritus and edema, but they have not proved very helpful in either the prevention or the limitation of most of the other lesions of the skin.

ORAL LESIONS

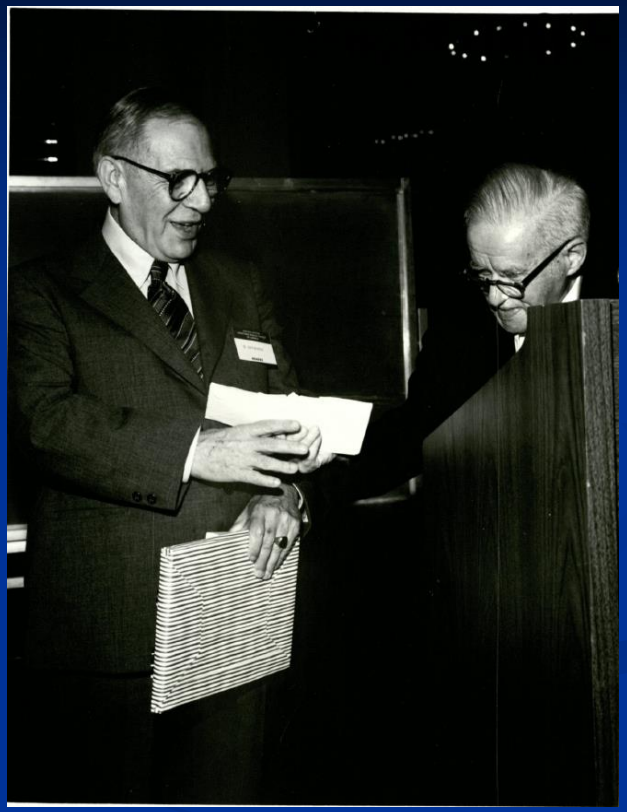
As many as 33 different oral manifestations have been reported[1] among the reactions to antimicrobial agents but most often with the broad-spectrum antibiotics, — aureomycin, chloramphenicol, terramycin, — and are sometimes described as ulcera-

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, and from the John C. Haynes Memorial and Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

The subject matter of this paper was presented under this title at the Eleventh Annual New England Post-Graduate Assembly, October 28, 1952, and also under the title "Untoward Reactions to Chemotherapy" at the Seventh Post-Graduate Lecture Course of the Massachusetts Medical Society, March 3, 1953. The essentials of both presentations are summarized here at the request of the editor.

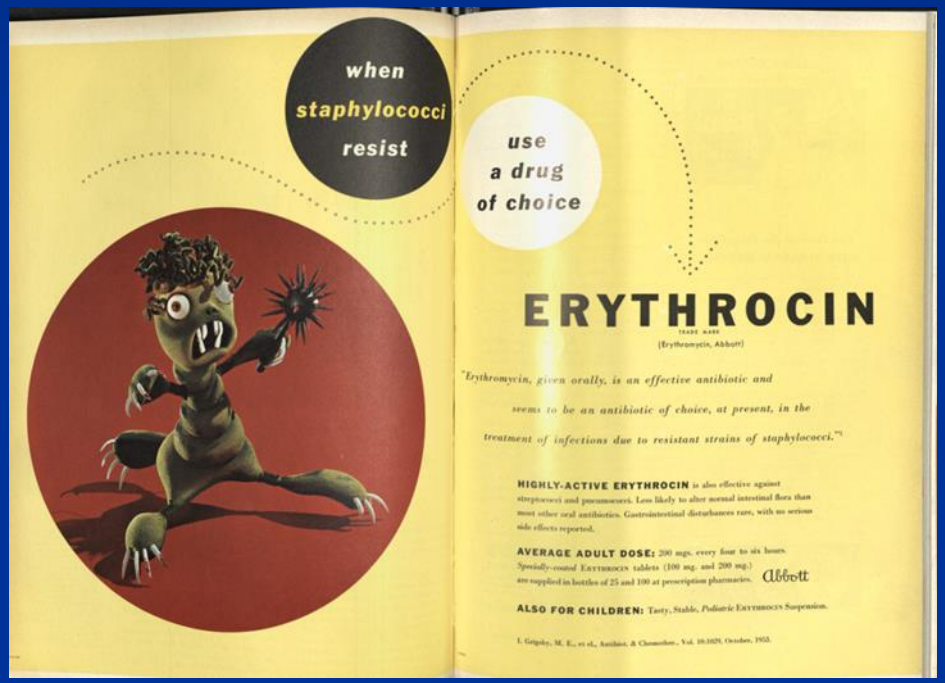
†Associate professor of medicine, Harvard Medical School; associate director, Thorndike Memorial Laboratory, and chief, Fourth Medical Service (Harvard), Boston City Hospital.

‡Associate professor of medicine, Boston University School of Medicine; lecturer in medicine, Harvard Medical School; chief of service, Department of Infectious Disease, Massachusetts Memorial Hospitals.



Louis Weinstein, 1908-2000

Source: Maxwell Finland Papers, Countway Medical Library


when staphylococci resist
use a drug of choice
ERYTHROCIN
TRADE MARK
(Erythromycin, Abbott)
"Erythromycin, given orally, is an effective antibiotic and seems to be an antibiotic of choice, at present, in the treatment of infections due to resistant strains of staphylococci."1
HIGHLY-ACTIVE ERYTHROCIN is also effective against streptococci and pneumococci. Less likely to alter normal intestinal flora than most other oral antibiotics. Gastrointestinal disturbances rare, with no serious side effects reported.
AVERAGE ADULT DOSE: 200 mgs. every four to six hours. Specially-coated ERYTHROCIN tablets (100 mg. and 200 mg.) are supplied in bottles of 25 and 100 at prescription pharmacies.
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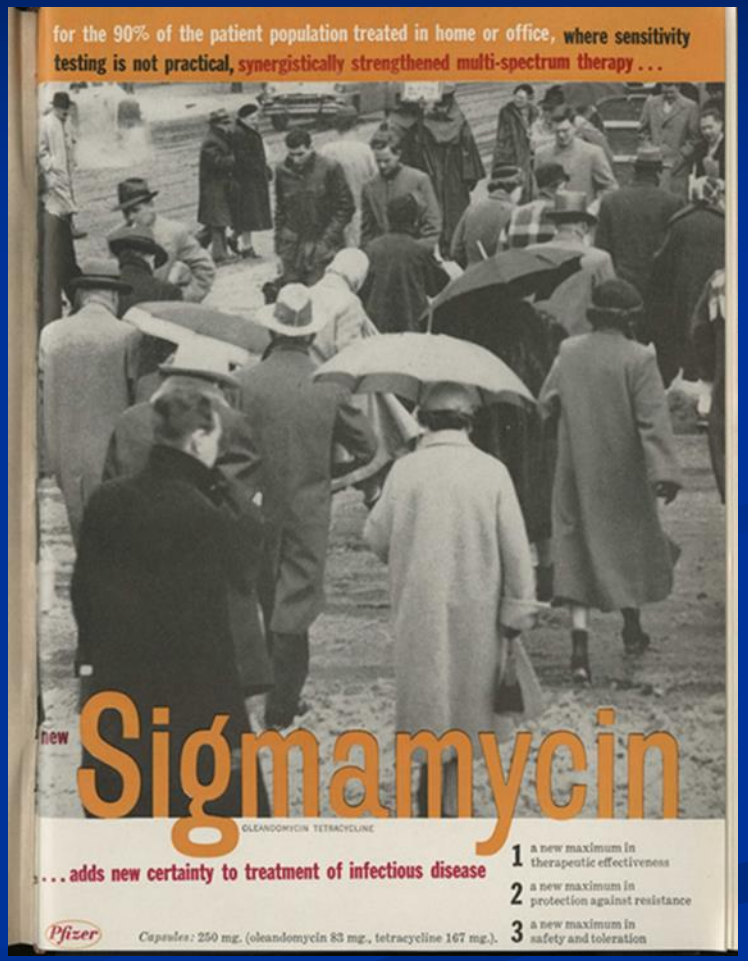
1. Grigsby, M. E., et al., Antibiot. & Chemother., Vol. 10:1029, October, 1953.


for the 90% of the patient population treated in home or office, where sensitivity testing is not practical, synergistically strengthened multi-spectrum therapy . . .
new
Sigmamycin
OLEANDOMYCIN TETRACYCLINE
. . . adds new certainty to treatment of infectious disease
1 a new maximum in therapeutic effectiveness
2 a new maximum in protection against resistance
3 a new maximum in safety and toleration
Pfizer
Capsules: 250 mg. (oleandomycin 83 mg., tetracycline 167 mg.).

Vancomycin, A New Antibiotic

III. Preliminary Clinical and Laboratory Studies

R. S. Griffith and Franklin B. Peck, Jr.

Lilly Laboratory for Clinical Research, Indianapolis General Hospital, Indianapolis, Ind.

A new microorganism, *Streptomyces orientalis*, was isolated from a soil sample obtained in Indonesia. An antibiotic recovered from the culture medium in which this actinomycete was grown was found to be primarily active against gram-positive cocci. Vancomycin* is the generic name given to this antibiotic. McCormick and his associates[1] have shown it to be relatively stable in acid media. Ziegler and his co-workers[2] have demonstrated it to be bactericidal in nature.

Our aim was to study the bacterial spectrum of this antibiotic and to confirm previous reports[1, 2] of the lack of development of resistance by *Micrococcus pyogenes* var. *aureus*. We were also interested in possible clinical uses for vancomycin. Consequently, the following studies were made.

RESULTS

Bacterial Spectrum. Fifteen species of organisms were used to test bacterial susceptibility to vancomycin (table I). Of 24 strains of *Streptococcus hemolyticus*, all were inhibited by concentrations of 0.156 to 2.5 μg./ml. of vancomycin. Forty-one of 43 strains of *M. pyogenes* var. *aureus* were inhibited by dilutions of 0.156 to 1.87 μg./ml. of the antibiotic. The 2 strains that were resistant to vancomycin were susceptible to penicillin and erythromycin. Six strains of penicillin-resistant staphylococci were included in the series, and all were sensitive to vancomycin. The 3 erythromycin-resistant strains were also found to be inhibited by vancomycin.

Other species in which we found sensitive organisms included *Streptococcus viridans, Streptococcus pneumoniae, Micrococcus pyogenes* var. *albus, Sarcina lutea,* and *Streptococcus faecalis*. Slight sensitivity was noted toward 1 strain of *Aerobacter aerogenes* and one strain of *Neisseria catarrhalis*.

Staphylococcal Resistance to Vancomycin. The development of resistant staphylococcal organisms was studied by the serial subculture method. Ten strains of *M. pyogenes* var. *aureus* were used, all of which had been isolated originally from purulent material. A technique similar to that used by Haight and Finland[3] was employed. Each strain was subcultured 25 times in media containing varying concentrations of vancomycin (fig. 1). The inhibitory concentration of vancomycin was considered to be that which produced complete prevention of growth of the test organism. It was found that resistance did not develop in the 10 strains of *Staphylococcus aureus* used for the study.

Preliminary Clinical Studies. We have found that vancomycin can be adminis-

* The trade name of Eli Lilly & Co. for vancomycin is Vancocin.

Antibiotics Annual (1955-1956): 619-622

Vancomycin, a New Antibiotic

IV. Pharmacologic and Toxicologic Studies

R. C. Anderson, H. M. Worth, P. N. Harris, and K. K. Chen

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A new antimicrobial agent, vancomycin,* has been isolated in these laboratories from strains of *Streptomyces orientalis*. Studies on the production, purification, and biologic activity were published previously by McCormick et al[1] and Ziegler et al.[2] Griffith and Peck[3] reported the preliminary clinical data. Vancomycin has been shown to be bactericidal at low concentrations and to be effective against antibiotic-resistant microorganisms. Development of resistant strains during therapy has not been observed. Because the antibiotic has continued to show promise in the chemotherapy of infectious diseases, various pharmacologic and toxicologic studies have been undertaken.

EXPERIMENTAL METHODS

Freshly prepared aqueous solutions of appropriate concentrations were used, vancomycin hydrochloride being soluble to the extent of 200 mg./ml. The *p*H varied from 1.8 for some of the early lots to 5.8 for the more recent ones.

Acute Toxicity. A total of 160 mice, 75 rats, 35 guinea pigs, and 8 dogs were injected by various routes after being deprived of food overnight. Concentrations of the solution were adjusted so that appropriate volumes were used. All animals were observed for one week after injection, and deaths were recorded. The LD_{50} was computed by the method of Bliss.[4]

Chronic Toxicity. Studies were made in four species. Three groups of 5 female rats each were injected subcutaneously daily for 29 weeks. In addition, 9 female mongrel dogs were injected intravenously each day for various periods. Blood samples were taken from the jugular vein for hematologic studies, and urine was collected by catheterization at biweekly intervals for analyses. Six rhesus monkeys were administered daily doses by vein for 16 to 187 days. Blood samples were also obtained for similar studies. Six cats were given intramuscular doses daily for three months and observed for any eighth nerve damage, according to the method of Molitor.[5] All animals were submitted for complete gross and histologic examination at death or on sacrifice.

Anaphylaxis. Nine guinea pigs were given an initial dose subcutaneously and challenged by an intravenous injection 25 days later.

Effect on Blood Pressure, Respiration, Intestinal Motility, Electrocardiogram, and Urinary Flow. Five dogs were anesthetized with phenobarbital sodium and observed for changes in blood pressure, respiration, intestinal motility, and electrocardiogram. The ureters of 3 dogs were cannulated and the urine flow recorded.

* The trade name of Eli Lilly & Co. for vancomycin is Vancocin.

Antibiotics Annual (1956-1957): 75-81

Second Era, 1963-1981

INFECTIVE HEREDITY OF MULTIPLE DRUG RESISTANCE IN BACTERIA

TSUTOMU WATANABE

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INTRODUCTION

In civilized countries, bacillary dysentery is no longer an important disease but in areas where public health is underdeveloped it still presents a serious problem. It seems rather paradoxical that in Japan, where sanitary conditions are considered to be fairly good, bacillary dysentery is still one of the most important infectious diseases. This is apparently due to the development of bacterial strains highly resistant to drugs. Shortly after World War II, a high incidence of sulfonamide-resistant shigellae appeared, and, since 1957, shigella strains with multiple drug resistance have been isolated with increasing frequency each year. This multiple drug resistance involves streptomycin (Sm), chloramphenicol (Cm), tetracycline (Tc), and sulfonamide (Su). A small proportion of these *Shigella* strains are resistant to only some of the drugs but the majority are resistant to all. Since these drugs are our most powerful chemotherapeutics against dysentery, the phenomenon of multiple drug resistance creates a serious problem in the therapy of this disease.

In 1959, it was found by Japanese investigators (5, 6, 89) that multiple drug resistance can be easily transferred between shigellae and *Escherichia coli* by mixed cultivation. This discovery led many Japanese workers to the genetic study of multiple drug resistance. We have found (115, 123, 124, 125, 131) that the multiple drug resistance factors are carried and transferred by an episome (17, 47, 50). Multiple drug resistance is, therefore, an example of "infective heredity" (Zinder, 147; Lederberg and Lederberg, 61). Investigations of the biochemical mechanisms of multiple drug resistance indicate that, at least with Su, Cm, and Tc, the resistance is due to reduced permeability of the cells to the drugs.

Initially, the problem of multiple drug resistance received attention because of its medical importance, but more recently much effort has been devoted to genetic studies from which the episomal nature of the responsible factors is

Bacteriological Reviews 27 (1963): 87-115

Are germs winning the war against people?

RECENT REPORTS in medical journals and the press warn that the problem of controlling infectious disease caused by bacteria may be getting out of hand. The first break in our defenses against bacterial infection appeared almost as soon as "wonder drugs" were developed, with the discovery of bacteria that were resistant to the new antibiotics. Now, scientists have found that many types of bacteria have acquired the ability to *pass* this resistance on to each other faster even than people spread germs in epidemics.

Medical authorities regard this situation as the most serious development in the field of infectious disease over the past decade—for a reason that has not been sufficiently stressed in press reports: Bacteria can spread their resistance not just to one but to *several* antibiotics at a time. And the bitterest irony of all is that the use of antibiotics actually aggravates this situation.

Doctors can no longer afford to prescribe antibiotics as freely as too many have been doing for too long. Some scientists feel that the use of antibiotics must be sharply curtailed in medicine and in the meat- and poultry-raising industries as well. If not, they say, we may find ourselves no better off than we were in the 1930's, before the advent of sulfa drugs and penicillin, when cleanliness was about the only weapon we had against bacterial infection.

This situation has many medical authorities deeply worried. It is so new that the problem of controlling it cannot yet even be defined. This is particularly disconcerting because the germs involved can cause everything from food poisoning and typhoid fever to cholera and plague.

The problem of transmissible bacterial drug resistance was thought, as late as 1962, to be confined to the Far East. Since then, it has popped up in Germany, Israel, Britain, Holland, Switzerland, Greece and—most recently—the United States. The first news of contagious bacterial drug resistance in this country appeared in the July 2 issue of *Lancet*, a British medical journal. It came from the Harvard Medical School, where Dr. David H. Smith reported that this was the most common form of drug resistance in a wide variety of bacterial infections he had examined in Boston hospitals. Dr. Smith believes it presents a serious hazard to the public health and urges that a national survey of the problem be undertaken.

The story of how medical scientists discovered the problem goes back to the 1950's, when Japanese bacteriologists were studying the *Shigella* bacterium's resistance to antibiotics. This bacterium is a principal cause of dysentery.

Classically, bacteria become resistant to an antibiotic by mutating, or changing, their hereditary makeup, so that the drug does not kill them. For example, one out of approximately every hundred million bacteria will mutate to resist the effects of streptomycin, even in the absence of the drug. In the presence of the drug, however, the resistant bacterium has a survival advantage over its vulnerable neighbors, which succumb. The mutant bacterium then has a clear field in which to multiply and build up a population of cells that are completely resistant to streptomycin.

Japanese scientists discovered in 1955 that some *Shigellae* bacteria were resistant not just to one but to three or four very different drugs: sulfonamides, streptomycin, tetracycline and chloramphenicol. The mutation theory did not apply. It would account for the development of resistance to *one* drug at a time, not three or four at once.

In addition, Japanese doctors discovered that some dysentery patients carried both *Shigellae* bacteria that were resistant to three antibiotics, and another very different bacterium that was resistant to the same three drugs.

Those two observations made it appear that resistance to several antibiotics at once was actually being passed from one bacterium to another in "packages" of three or four resistance traits.

Not only are germs developing resistance to "wonder drugs," but they're passing on this resistance to each other

Japanese bacteriologists proved this theory in 1959. Scientists later learned that the packages of multiple drug resistance could, themselves, multiply in bacteria, and that they were passed from cell to cell on contact. The resistance traits apparently achieve their protective effects by preventing certain antibiotics from getting into the bacterial cell.

Scientists do not yet know where drug-resistance traits come from. They do know that they exist in many kinds of bacteria. They also know that bacteria that are sensitive to drugs can "catch" from other bacteria resistance to *all the most effective antibiotics used in medicine today.*

Dr. E. S. Anderson of Britain's Public Health Service has even found a Superbug that carries resistance to more than seven powerful antibacterial agents: streptomycin, tetracycline, chloramphenicol, sulfonamides, neomycin, kanamycin and the penicillins.

What causes bacteriologists great concern is the prospect that such a bug might get loose and create an epidemic of invulnerability to drugs among germs throughout the world. This could conceivably happen if the spread of these multiple-resistant germs is not checked.

Studies in Japan and Britain have shown unequivocally that the use of antibiotics encourages the spread of multiple-drug resistance factors in bacteria. For example, suppose that a few of Dr. Anderson's Superbugs were lurking in a mass of bacteria sensitive to tetracycline. Administration of that antibiotic would kill the sensitive germs all right, but a host of Superbugs would be spawned as a consequence.

Sparing use of antibiotics would lessen the spread of bacterial drug resistance. Also, because the resistance traits are unstable, and frequently disappear spontaneously, not bringing them out with antibiotics may eventually make them vanish.

There is no doubt among authorities that the rise in the number of multiply-resistant bacteria is due largely to the imprudent use of antibiotics in medicine and their widespread use—for treating and preventing infection—in the raising of cattle and poultry. This latter application has greatly improved the quantity and quality of meat in this country; it is uncertain what effect curtailing the use of antibiotics would have on meat production.

Nevertheless, Dr. Anderson, who has studied bacterial drug resistance in cattle fed on antibiotic-treated feed, has declared that "The time has clearly come for a reexamination of the whole question of the use of antibiotics and other drugs in the rearing of livestock."

And Dr. Naomi Datta of the Postgraduate Medical School of London, where she has studied the problem in humans, insists that "antibiotics should be reserved for when really necessary."

Meanwhile, the pharmaceutical industry is working harder than ever to develop *new* antibiotics so that we can at least stay even in the war against our bacterial enemies.

JOHN A. OSMUNDSEN

DRAWING BY JAMES FLORA

Look Magazine, November 1966

to (a) abstracts published in connection with meetings, or (b) press reports resulting from formal and public oral presentation.

ENVIRONMENTAL POLLUTION WITH RESISTANT MICROBES

THE do-no-harm doctrine, fundamental to most physicians, is often unwittingly relegated to secondary status by the understandable human desire to "do something." The unfortunate consequences of this reversal of priorities are nowhere better catalogued than in the chronicles of antibiotic usage, where three decades of secondary catastrophes are recorded. The phenomena resulting from the toxicity and hypersensitivity induced by these miracle drugs exhibit their mark in every bodily organ, cell and orifice. To wager today that any new antimicrobial agent will be completely safe, regardless of its alchemy, is to ignore the laws which make paupers of chronic roulette enthusiasts.

The untoward effects awaiting the drug recipient himself would be sufficient reason to heed the dire words used by the antagonists of promiscuous antibiotic therapy to warn against its inherent hazards. In the current issue of the *Journal*, however, two articles exemplify a problem with a far more anxious portent: that of changing the entire microbial ecology to one generally resistant to available antibacterial agents.

The first report, by Aserkoff and Bennett, on the fecal excretion of salmonellae is an illustration of how antibiotics not only may fail in their intended purpose but may give rise to the exact problems they were supposed to prevent. Fearing a major epidemic, local health officials advised the administration of either ampicillin or chloramphenicol, 1 gm daily for three days, to several hundred victims of a *Salmonella typhimurium* food-poisoning outbreak. Rather than aborting the fecal output of salmonellae, as the authorities had hoped, the antibiotics seemed to encourage prolonged postconvalescent excretion. Of the patients who received therapy, more than twice as many were continuing to shed organisms a month later when compared to a group who did not receive any antimicrobials. At least as important, however, was the finding that nearly 10 per cent of the strains of salmonella recovered from patients exposed to drugs were resistant in vitro to multiple antibiotics (the original offending strains were not), and that this resistance was largely transferable to sensitive organisms. The increased hazard to possible recipients of these resistant forms and the potential for widespread dissemination of antibiotic-resistant salmonellae, already noted in England,[1] are frighteningly obvious.

Although the implications of the data presented by Askeroff and Bennett are important, the information on which their report is based is not wholly interpretable. The amounts and duration of antibiotic treatment recommended and used were perhaps quite inadequate and might actually have encouraged persistence and the development of resistance. Herrell[2] has suggested that treatment of salmonella gastroenteritis, with much larger doses and for longer times, is still indicated in some patients, particularly those peculiarly susceptible to systemic invasion by the salmonella. Some reports, however, in which a more extensive treatment program was employed,[3,4] lend support to the thesis advanced by Askeroff and Bennett, and it is obvious that more rigorously controlled trials are needed to resolve these differences of opinion. It would also be worth learning from a sufficiently large series of patients whether adequate antimicrobial treatment affects the development of the true chronic salmonella carrier state.

The other study in this issue is by a group of Danish workers with sufficient patience (and storage space) to observe staphylococcal disease and to study the responsible organisms collected throughout their country over a 10-year period. It indicates clearly that the dominant staphylococci responsible for disease in hospitals are selected by the pressures of the antibiotics used in the environment and that the shifts in staphylococcal phage patterns are associated with a broadening of their antibiotic resistance patterns. The "simple rule" of these investigators that "strains sensitive to an antibiotic can hardly maintain or gain a dominating epidemic position in environments in which this antibiotic is extensively used" is a sufficiently elementary exposition of the experience in our own country over the past 25 years.[5] Their general observation that antibiotic resistance is associated with a less favorable outcome in bacteremia should, regardless of the underlying reasons, engender appropriate concern.

Antibiotics must, of course, be used. When applied appropriately, they relieve suffering and prevent death. But their application should be carefully scrutinized and based on reasonably sound principles. Man has succeeded in polluting his environment with an astonishing variety of noxious agents. The development of an antibiotic-resistant microbial milieu might be a logical extension of this self-directed biologic warfare, but it is doubtful if many physicians would wittingly subscribe to such an idea. Perhaps it is time to wonder whether the unwitting accomplishment of the same end, without critical appraisal, is any less serious an offense.

RICHARD A. GLECKMAN, M.D.
MORTON A. MADOFF, M.D.

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ety can be performed; decision on the donating of eyes or other tissues that can restore lost functions to the living.

Whatever one may believe about a life after death, one can scarcely deny that the memory left in the thoughts of those still living provides a means of achieving some part of it.

As penned by an unknown author:

> We cannot know the ending of the path,
> Nor quite accept its regimented bliss,
> Devoutly planned for life's long aftermath,
> Nor hold to any certain thing, save this:
> They have not gone, nor can they dwell apart,
> Who still have place within some living heart.

INFECTIOUS DRUG RESISTANCE

SINCE the inception of antibiotic therapy, the dramatic healing power of antimicrobial agents has been threatened by the ever more insistent emergence of antibiotic-resistant bacteria. Some of the clinical[1] and biologic[2] problems posed by this phenomenon have been summarized recently. Until lately, the principal mechanism responsible for drug resistance was thought to be spontaneous mutation at a low rate to a particular drug resistance followed by selection of resistant cells in the presence of the drug.

Although threatening enough, this mechanism is slow and cumbersome in comparison with infectious multiple drug resistance, a newly discovered process that is intellectually fascinating and therapeutically frightening. First recognized in Japan in 1959, infectious multiple drug resistance is a process by which sets of genes determining resistance to several unrelated antibiotics are transferred together from resistant to sensitive strains by cell-to-cell contact.

These genes are not located on the bacterial chromosome, but on extrachromosomal genetic elements called R factors, which are composed of DNA but replicate autonomously. R factors contain a region called RTF (resistance-transfer factor) that determines infectivity and to which the separate drug-resistance genes are attached. R factors resemble viruses without coats, but they are also modified sex factors since they mediate their own transfer from cell to cell.

Transfer occurs not only within species of the enteric bacteria but also between groups as diverse as shigella, salmonella, klebsiella, vibrio, pasteurella, serratia and the ubiquitous *Escherichia coli*, which can serve as a reservoir. Indeed, *Esch. coli* is of key importance in facilitating transfer of R factors from one pathogen to another and from animals to humans.

An analogous situation exists in the staphylococci, where antibiotic therapy has been notoriously difficult. Genes for resistance to penicillin, erythromycin, tetracycline, chloramphenicol and kanamycin are carried on extrachromosomal particles called plasmids.[2] No RTF's have been found, but plasmids are transferred from cell to cell by phages. It may be the rapid emergence of drug resistance among the staphylococci is related to the dissemination of plasmids by phage transduction.

The first report of R factors outside Japan came from Great Britain in 1962,[3] and by 1965, extensive surveys of their distribution as well as studies of their fundamental properties had already been carried out there[4,5] as well as in Japan[6]; R factors had also been reported in other European countries and in Israel. However, the first clinical study of R factors in the United States, by Kabins and Cohen, appears elsewhere in this issue of the *Journal*, and similar studies are in progress in Boston and New York. These investigations stress the present widespread occurrence of enteric bacteria harboring R factors in this country. And they emphasize the threat to antibiotic therapy posed by these infectious agents as well as the need to monitor their spread.

Both Japanese and British studies have correlated the precipitous rise in frequency of R factors with the increasing use of antibiotics not only in clinical practice but also in the care and feeding of livestock. Antibiotics are now incorporated routinely in livestock feeds, providing a constant selection pressure on R factors that can be readily transferred to man. It appears that unless drastic measures are taken very soon, physicians may find themselves back in the preantibiotic Middle Ages in the treatment of infectious diseases.

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POST-TRANSFUSION PURPURA

A SIXTH case of post-transfusion purpura is described by Morrison and Mollison in this issue of the *Journal*. The infrequency with which this disorder occurs places it rather low among the various causes of postoperative thrombocytopenia, but some of its implications deserve consideration. Morrison and Mollison suggest that part of the antibody produced in response to the $P1^{A1}$ platelet antigen crossreacts with a structurally similar antigen on autologous platelets, resulting in thrombocytopenia and absorption from the circulation of the crossreacting antibody fraction and thereby rendering it

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 130, NO. 2 • AUGUST 1974

Usage of Antibiotics in a General Hospital: Effect of Requiring Justification

John E. McGowan, Jr. and Maxwell Finland

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The amounts of certain antibiotics used at Boston City Hospital during recent years have been reviewed and correlated with the requirement to justify the choice of those antibiotics. This mild restraint on the prescribing of antibiotics for hospitalized patients appears to have substantially limited the use of certain potentially toxic or expensive agents, and removal of that restriction has been followed by an increase in use of those agents. Similar, relatively simple requirements may promote more effective and economical use of antibiotics and perhaps of other classes of drugs.

Many antimicrobial agents have the potential for producing serious toxic reactions, and some may also be associated with ready emergence of resistant pathogens in the patient and his environment. To minimize these problems, the use of a number of systemic antimicrobial agents at Boston City Hospital has been restricted; the prescribing physician is required to notify a member of the Infectious Diseases Unit and to justify the choice before the drug can be dispensed for the patient from the hospital pharmacy. During the period that this policy has been in effect, a number of antibiotics have been added to, or deleted from, the restricted list. This paper examines the changes in usage of antibiotics during the period 1965–1972, with special reference to some of the agents that were removed from the restricted list, and to others that either were placed on the list during this interval, or had remained on the list.

Historical Background

At the Boston City Hospital the safety and efficacy of most of the major new antibacterial agents have been clinically investigated as they became available. The agents were provided by their producers; they were administered under careful control, and guidance was provided to physicians in their proper use and in observation of the patients' responses. This was done with the full knowledge and consent of the patients (as far as possible) and of their physicians. After the new drugs were marketed, observations on efficacy and safety continued.

The hospital purchased new antimicrobial drugs only on recommendation of its Infectious Diseases and Pharmacy Committees. These committees review the approved list of antimicrobial drugs in use at least once each year, paying particular attention to the ones whose potential for toxicity or for causing emergence of resistance among organisms prevalent in the hospital or whose high cost warrant some restriction on their use. Such drugs are placed on a restricted list that requires only that ordinary criteria of good usage be met for their release by the pharmacy. In practice the simple procedure used to implement this restriction has served not only as a deterrent against abuse of certain antibiotics, but has also provided continuing education of the hospital staff (and the consultants) in the proper use of those agents in the management of their patients.

Role of the Infectious Diseases Unit

A physician from the Infectious Diseases Unit is available for consultation 24 hours a day, includ-

Received for publication September 29, 1973, and in revised form March 25, 1974.

This study was aided in part by grants no. 5R01-AI-23 and 2T01-AI-68 from the National Institute of Allergy and Infectious Diseases. We are indebted to Anthony Ricciardone for help in obtaining the data on drug usage.

Please address requests for reprints to Dr. Maxwell Finland, Channing Laboratory, Boston City Hospital, Boston, Massachusetts 02118.

Are Family Doctors Prescribing Too Many Antibiotics?

NEA D'AMELIO, Associate Editor

Antibiotic use held excessive

Physicians are over-prescribing antibiotics, resulting in resistant strains of bacteria and an increased number of "superinfections," the director of FDA's Bureau of Drugs told the Senate Small Business monopoly subcommittee.

"There may be 100,000 to 300,000 cases each year (of blood poisoning from superinfections), of which 30% to 50% are fatal," said Henry E. Simmons, MD.

FDA last week started to set up an advisory committee on antibiotic use.

Harry F. Dowling, MD, emeritus professor of medicine, U. of Illinois, said, "It is doubtful the average person has an illness that requires treatment with an antibiotic more often than once every five or 10 years." Antibiotic production has needlessly increased, however, in the past 10 years, he said.

The physician's fear of failure to help his patients—stronger than his fear of complications—motivates him to prescribe antibiotics, suggested Calvin N. Kunin, MD, of the U. of Wisconsin School of Medicine.

The AMA News story, reproduced above, prompted us to mail a questionnaire to 10,000 family physicians in private practice and 10,000 residents in hospitals across the country. We wanted to know what "the accused" had to say about the allegations. We were deluged with replies: 5,331 MEDICAL TIMES readers (an incredible 53%) and 2,358 residents (24% of those queried) answered the questions we sent them. (See Tables I and II for a statistical look-see at how they voted). Interestingly enough, and perhaps not surprising, family doctors were divided in their opinions about the over-prescribing of antibiotics, but 9 out of 10 of the residents surveyed think that physicians in private practice *are* over-prescribing antibiotics—and significantly so.

Perhaps it's the "generation gap" that's showing, but it's worth noting here and now the following comment from a private practitioner:

"I happen to serve as a student health director and I've noticed that the older doctors usually do prescribe antibiotics more freely than the younger doctors—but, on the other hand, their patients usually lose

"I wonder if the Emeritus Professor ever was obliged to cure a stevedore of acute tonsillitis while the patient is working full time."

fections often turn into fulminating ones with severe after effects such as rheumatic fever and acute glomerulonephritis. If the FDA would stay out of medical research and stop interfering, more and better antibiotics could be discovered to take care of resistant strains."

The charge that doctors' over-prescribing antibiotics were resulting in resistant strains of bacteria and an increased number of "superinfections" came under sharp attack by over 100 respondents.

From Illinois, a family physician commented: "The real factor to consider is how many of these resistant or superinfective organisms actually prove to be a significant primary pathogen to persons of average health. In other words, are we creating *new* infective organisms for the general population by treating with antibiotics in the 'generally accepted manner' of today? Are we making more trouble than we are clearing up or preventing? I think *not*, in the absence of some trustworthy studies to the contrary, despite what a few power-hungry physician-bureaucrats, or forgetful, retired professors of medicine may say."

And another family physician in the midwest wrote: "Resistant strains are caused by the *under* use of a particular antibiotic on a particular germ. In other words, not getting the infection completely killed, leaving the more resistant germs to propagate and spread to other people. Never use antibiotics half way. But when you do, use them enough to really do the job."

Typical of more than 300 family doctors who wrote with little warmth or sympathy for the testimony of FDA doctors was this note from a Texas diplomate in Family Practice: "I'll tell you the only thing I think is being overprescribed and that is a hell of a big over-dose of government being rammed down the esophagus of the medical profession. Like any other OD, it's either going to injure or kill the patient—in this case, yours and my profession."

FDA MDs Are Not in the 'Front Lines'

In answering the second question, "Do you agree (with the emeritus professor of medicine) that the average person does not require antibiotics more than once in every five or ten years," almost 90% of our family practitioners answered No—and with a great deal of emphasis! On the other hand, our resident respondents were divided with 55% voting Yes. Here's a rundown of some "quickies":

- "Such statements as these are from men who are not on the firing line of practice."
- "Send these men out to rural South Dakota to practice medicine and see if they don't change their minds."
- "This question hinges on the word 'require'—nobody 'requires' antibiotics, I suppose, but they *are* cheaper than funerals."

Medical Times 102 (1974): 53-61

List of Premises

1. Educators do not treat patients but may be very knowledgeable about antibiotic usage. Physicians may not be well informed on use of antibiotics. Therefore, peer review may be useful.

2. Physicians do not want the major ruling on antibiotic usage to come from Washington.

3. The foremost drive for manufacturers to market antibiotics is the profit motive.

4. The duty of the hospital pharmacist is to see that the right amount of drug is given to the patient at the right time.

5. To be used properly, antibiotics should be used for bacterial infections and should not be used prophylactically.

6. Laboratory cultures should precede use of antibiotics.

7. It is the uncommon patient with the uncommon cold that sees a physician. Therefore, antibiotics may be justified in this clinical setting.

8. Use of large amounts of antibiotics in itself may not be bad.

9. Antibiotics can be prescribed over the phone without a culture.

10. A level of antibiotic usage that would constitute appropriate efficacy can be determined.

11. Inappropriate use of antibiotics exposes the patient to dangers of the antibiotic without really giving him any of the advantages.

12. Use of antibiotics in hospitalized patients may affect the health and welfare of other patients in the hospital.

13. Use of antibiotics on clean surgical sites is not useful and may be harmful.

14. Obtaining a pre-treatment culture improves the appropriateness of antibiotic use.

15. Assaying antibiotic blood levels during therapy could improve therapy.

16. Antibiotics are prescribed more widely by physicians educated in the antibiotic era.

17. Fear of malpractice suits is forcing physicians to use more antibiotics.

18. The incidence of resistant gram-negative infections is growing and this may be due to antibiotic therapy.

Third Era, 1981-1988

STATEMENT REGARDING WORLDWIDE ANTIBIOTIC MISUSE

Antibiotics have been developed to treat diseases caused by micro-organisms in humans, animals, and cultivated plants. However, these antimicrobial agents are losing their effectiveness because of the spread and persistence of drug-resistant organisms. Moreover, unless steps are taken to curtail the present situation we may find a time when such agents are no longer useful to combat disease.

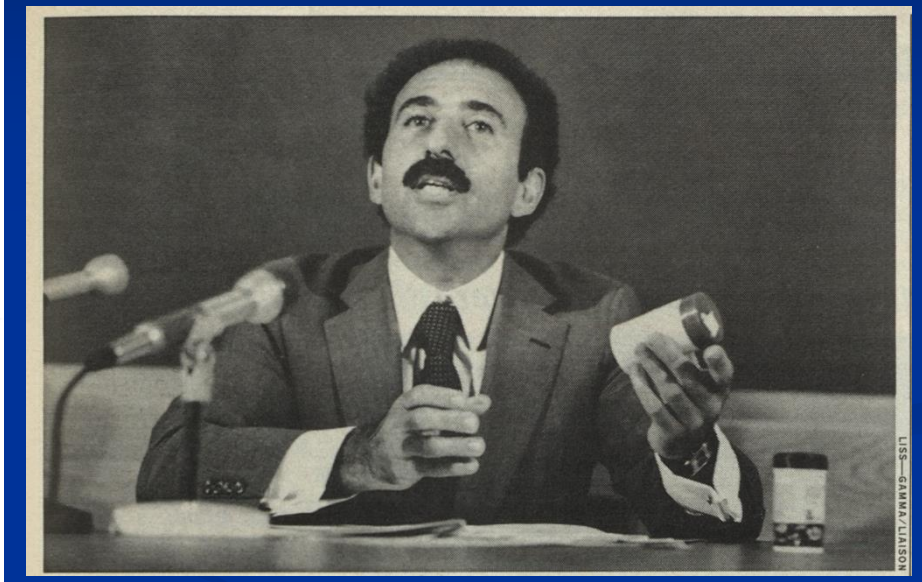
We are faced with a worldwide public health problem. It is due in large part to the indiscriminate use of antibiotics, especially in the following practices: a) dispensing antibiotics without prescription; b) using clinically-useful antibiotics as growth promoters in animal feeds and on agricultural crops; c) prescribing antibiotics for ailments for which they are ineffective; d) misleading consumers by advertising antibiotics as "wonder drugs," especially in areas where dispensing is not regulated; e) using different labeling and advertising to sell the same product in different parts of the world.

Let no one suppose that widespread use of antibiotics is in any way a substitute for good sanitation and personal hygiene. Efforts in improving these mainstays of infectious disease prevention and control must be encouraged and strengthened. At the same time, it is imperative to increase awareness of the dangerous consequences of antibiotic misuse at all levels of usage: consumers, prescribers, dispensers, manufacturers, and government regulatory agencies. Only then can we begin to institute measures to curb the unnecessary use and flagrant misuse of these drugs.

We, the undersigned, have drafted this statement to instigate action towards halting this ever-increasing worldwide problem. We would like this communication to serve as the impetus for organizing national and international

679

Molecular Biology, Pathogenicity, and Ecology of Bacterial Plasmids (New York: Plenum, 1981)



Photograph courtesy of Steven Liss

Stuart Levy, releasing the "statement" in Boston, 1981

APUA Newsletter

Alliance for the Prudent Use of Antibiotics

Vol. 1 No. 1 Summer, 1983

APUA: History and Goals

Since the initial discovery of antibiotics, scientists were concerned about resistant strains and predicted their emergence. What was not anticipated was the rapidity and extent of the change in the ecology of resistance plasmids which is now evident in our world environment. This situation is the direct result of massive use of antibiotics and a lack of restraint in their prescription and utilization.

Many have helped to establish *The Alliance for the Prudent Use of Antibiotics* whose present membership includes individuals from almost fifty countries of the world. The Alliance exists because of the response to a "Statement Regarding Antibiotic Misuse" issued in August, 1981. The Statement was the culmination of talks and discussions at a January, 1981, meeting in the Dominican Republic where over 200 research and medical scientists met to discuss the pathogenicity and ecology of bacterial plasmids. It became evident at the meeting that the rising incidence of antibiotic resistance plasmids in pathogenic bacteria, paralleled by the unexpectedly rapid increase in pools of resistance plasmids among common non-pathogenic bacteria, was of grave public health concern for the entire world.

The very establishment of the Alliance has brought recognition of the problem and provided a source for joining together in order to find solutions to this world health issue. Among the goals of the Alliance are the following:

1) Inform and educate, on a regular basis, the general public about the dangers of misusing and overusing antibiotics and other antimicrobial agents.
2) Inform and educate medical and para-medical personnel worldwide about the defined and specific action of antibiotics and the necessity of controlling their dispensation and prescription.
3) Provide data to individuals and organizations interested in preventing antibiotic misuse and overuse.
4) Promote an international policy for uniform antibiotic packaging that ensures clear descriptions of the indications for use, duration of use and possible side effects of the drug.

Our goals are not easy to achieve. We must reach and educate many different communities worldwide: medical, veterinary, pharmaceutical pharmacologic and the general public. Education into the "why's, where's and when's" of usage is imperative in order to forestay antibiotic obsolescence. Great consideration should be given to how new antibiotics will be introduced and used in a world where these agents have often been dispensed as readily and easily as aspirin.

Abuse and overuse take different forms and practices. Individuals and local groups must address the primary problem of their own country. Then, together with others, global antibiotic misuse can be curtailed. The World Health Organization has issued a document detailing the problems of antimicrobial resistance and making recommendations for standard practice in the prescription and utilization of these valuable agents. This publication "Antimicrobial Resistance Report of Scientific Working Group" (WHO/BVI/PHA/ANT/82.1) can serve as a standard for all who wish to join APUA in striving to achieve uniformity of practice.

Open communications with the World Health Organization, Pan American Health Organization and other international and national health organizations have been established. Through APUA, members will be kept aware of the advances in antibiotic development in the world and steps being taken to curtail abuse and misuse. Recommendations and advice will be sought on how to deal with the ever-increasing problem of resistance.

The initial means for achieving these aims will be this *Newsletter*, audiovisual educational materials and facilitation of the exchange of information among our members. When possible small research grants will be given for work related to these goals.

This inaugural issue of the APUA Newsletter initiates a firm commitment to provide current and historical perspectives and information on antibiotic usage and the problems of antibiotic resistance worldwide. It is established as a forum for transfer of information among members.

Thomas O'Brien, circa 1986

Credit: BWH Archives

Pharmaceuticals

NIH retreat from controversy

Washington

US RESEARCHERS are querying the cancellation by the National Institutes of Health (NIH) of a major international conference on the use of antibiotics and antibiotic resistance. Plans for the conference were laid five years ago, but pharmaceutical industry executives accused the organizers of spreading "propaganda" and of "obvious pre-judgement" of the issues. Plans for the conference have been repeatedly changed and delayed, and NIH director James Wyngaarden has now decided to substitute a small workshop of conference planners.

The conference, administered by NIH's Fogarty International Center, was finally to have taken place next month. Wyngaarden says his decision to convene instead a small workshop was made exclusively on the basis of a scientific review of conference planning documents by acknowledged experts. But Dr Jerry Avorn of Harvard University, one of the organizers, said the conference documents are "every bit as good as the prevalent high standards of NIH" and that he was "left wondering" if lack of scientific merit was the true reason for the cancellation.

After a preparatory meeting for the conference in September 1984 at which six task forces were organized to prepare working documents, several industry executives wrote to Edward Brandt Jr, then acting assistant secretary for health, protesting that the organizers were biased against industry. The conference would have covered misprescribing and overuse of antibiotics both in humans and in animal feed. M. Marion Jones, president of Beecham Laboratories, said that the conference organizers were simply trying to confirm the beliefs of a number of "activists" present and to secure endorsements of proposals by NIH and the World Health Organization, which was also involved in planning.

Among those present at the meeting were Dr Sidney Wolfe, director of the Public Citizen Health Research Group, Dr Andrew Herxheimer of Charing Cross Hospital (London) and editor of *Drugs and Therapeutics Bulletin*, published by the British Consumers' Association, and Ms D. Melrose of Oxfam, all of whom have expressed concern about misprescribing of antibiotics.

Thomas Christie, vice-president of medical affairs of Wyeth International Ltd, wrote of a "general anti-industry bias" and said that further meetings of one of the task forces would "culminate in an outright attack on free enterprise". Christie asked Brandt to "use the influence of your office to limit this activity".

Wyngaarden says he was alerted to concern about the conference by several individual members of conference planning groups; one, for example, wrote that an international conference would be premature because there are insufficient data. He then had several of the planning documents reviewed by experts (including himself) and four reviewers agreed the conference should be scaled down, although two recommended going ahead. Hopes for a large conference have not been entirely abandoned, however; the workshop next month may lay the groundwork for a large conference later. **Tim Beardsley**

Shcharanskii release triggers hopes

Stockholm

THE release from the Soviet Union last week of Anatolii Shcharanskii after nine years in prison for alleged espionage appears to have raised spirits not only in the West but also within the Soviet Union. In Moscow last Saturday, a group of refusniks at a special meeting to mark the 850th anniversary of the birth of the mediaeval scholar Moshe Ben Maimon (Maimonides) issued a statement hoping that "those who have been striving for the simple and natural right to live in Israel will soon be free to do so".

The Maimonides seminar was the biggest gathering of refusniks since 1980. More than 40 people took part, including two visitors from Scandinavia, Dr Jens Larsen of Denmark (who spoke of last year's Niels Bohr celebrations) and Dr Oyvind Gron of Oslo (who spoke on the expanding Universe).

Apart from abstracts of recent work presented by almost 30 refusniks, there was also a poster session which appears to have been stimulated by the efforts made in recent years by scientists in the West who have been seeking means by which refusniks might contribute to international conferences by means of posters displayed *in absentia*.

Ironically, the Moscow seminar almost coincided with a meeting held in London by the Institute of Physics to mark the ninth anniversary of the arrest of Dr Yurii Orlov, now exiled to Yakytria, Siberia. Since the expiry of Orlov's five-year prison sentence, there have been several campaigns to persuade the Soviet authorities to commute internal to external exile.

Last week, the British lawyer John Macdonald announced that he had now written to the Soviet authorities to argue that, since Orlov had now turned sixty (pensionable age in the Soviet Union), he should be allowed to settle in Britain. Vera Rich

IVF

India embraces test-tubes

New Delhi

ALTHOUGH population control remains India's chief objective in human reproduction technology, *in vitro* fertilization (IVF) is now also officially encouraged as a treatment for infertility. With the first test-tube baby on the way at the Kem hospital in Bombay, more than a hundred infertile couples are being treated at the private clinics springing up in Bombay and Madras as well as at the government-run All-India Institute of Medical Sciences, which has set up an IVF clinic here.

"With so many of our women wanting to go abroad for test-tube babies, we cannot ignore the need for treatment in India", says Dr Kamal Bukshee, the gynaecologist in charge of the All-India clinic. Although India may be oppressed by too many children, physicians are concerned that infertility, which is a significant problem in India, may be exploited by quack sexologists.

One of the British hospitals offering IVF treatment has recently appointed an agent in New Delhi to handle enquiries from Indian patients seeking treatment. According to Dr Bukshee, many of those enquiring are prevented from going abroad by the prohibitive cost. She has herself developed a variation of the standard technique in which ultrasound is used for scanning the ovary and locating ripe eggs, which are then removed by the use of a needle rather than by laparoscopy. She says that treatment can be offered in the outpatients' department of the hospital at a fraction of the cost that patients would have to spend if they went abroad.

In vitro fertilization was first sanctioned three years ago by the Indian Council for Medical Research, which after much hesitation began a programme of research at its Institute for Research in Reproduction (IRR) at Bombay. In collaboration with the Kem hospital, the institute has now perfected the method after trying it out with 25 women with blocked fallopian tubes. The first success was with a 30-year-old janitor who is now four months pregnant. This has so stimulated demand that a computer is now being used to store information about the women on the waiting list, and to choose which should have treatment.

Dr T.C. Amand Kumar, director of IRR, says that even if all the women now seeking treatment were to become pregnant, "there will be no undesirable effect on our population", but that IVF technology will have beneficial effects in medicine as a whole, especially in the treatment of inherited diseases by gene therapy. **K.S. Jayaraman**

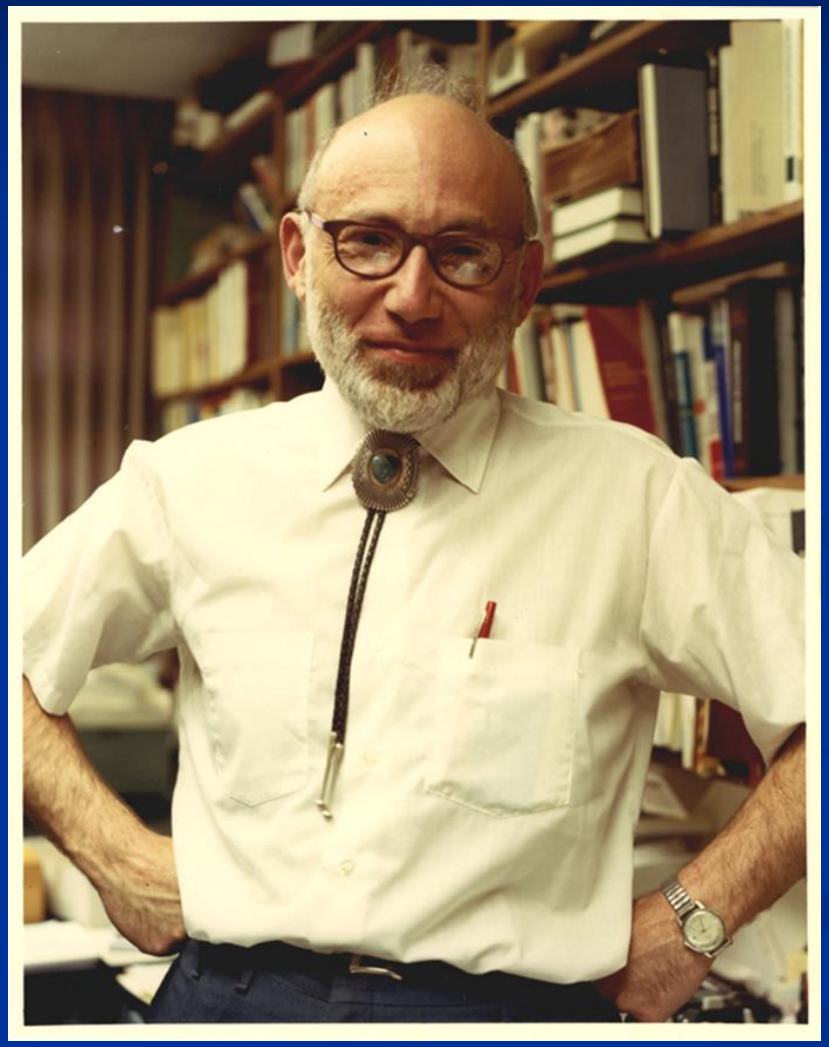
Nature 319 (1986): 611

"Some influential critics from industry believed that such an activity cast wrongful doubts on the efficacy of their antibiotic products … [The Task Forces] … were disregarded and even downplayed under the guise that the problem was being overstated."

Stuart Levy

From *The Resistance Phenomenon in Microbes and Infectious Disease Vectors* (Washington: National Academies Press, 2003)

Fourth Era, 1988-present



Joshua Lederberg, 1925-2008

Image from the National Library of Medicine

Joshua Lederburg

Mankind Had a Near Miss From a Mystery Pandemic

IN THE aftermath of the six-day war in the Middle East last summer, direct air transport from Uganda to Germany and Yugoslavia was disrupted. Shipments of "green monkeys" for use in preparing vaccines were diverted to London airport before transshipment.

In the process, a group of at least eight monkeys acquired a disease heretofore unknown to medical science. The disease remains unnamed but might be called Marburgvirus, for it infected at least 32 people and killed five of them in Marburg, Germany, and infected two in Frankfurt.

Twenty-seven of the infected cases were among laboratory workers who handled the monkeys or their organs. Five were secondary cases, nurses or doctors who attended the primary ones and were in direct contact with the patients' tissues or secretions. In a brief review in Nature magazine, Dr. C. E. Gordon-Smith, director of the British biological warfare research laboratory at Porton, also alludes to the transmission of Marburgvirus as a venereal disease, but this is perhaps conjectural.

THERE IS, however, no doubt that Marburgvirus is extraordinarily contagious and rapidly lethal in a distressingly high proportion of cases. It is found in the blood, throat secretions and urine of infected animals and men and direct contact is the only known medium of transmission. What might have been an epidemic of world-shaking dimensions was contained by the sheer good luck that it did not spread to man at London airport but first appeared in the medically knowledgeable environment of the laboratory destinations.

The Porton laboratory was involved when the unusually contagious character of the new disease was first realized by the German physicians. As its director remarks, "The facilities for the study of infectious diseases are of a kind probably unmatched in Western Europe; there is a strict code of safety and specially designed apparatus to cope with hazardous operations. Elaborate precautions are taken to prevent the escape of infective material and a research section is devoted solely to the study of laboratory hazards."

Its scientists were then especially prepared for the further experimental study of the new disease. They soon showed that the Marburgvirus was quite distinct from any previously known disease agent and quite unresponsive to every antibiotic tried.

The virus is also under study in Johannesburg and in the United States Public Health Service researchers at the Communicable Disease Center at Chamblee, Ga., have confirmed that it is a new virus though possibly related to the vesicular stomatitis of cattle.

THE ORIGIN of Marburgvirus is unknown. It may be indigenous to green monkeys in Africa; it may have been acquired by contact with other animals in whose company the monkeys were held during transshipment through London.

The threat of a major virus epidemic—a global pandemic—hangs over the head of the species at any time. We were lucky on this occasion, but it was a near miss. It could easily have established a very large focus of infection in countries like India or China or South Vietnam, and in our present knowledge of virology we would have been ill-equipped to stop it from dominating the earth, with a half-billion casualties.

We have also seen the irony of the constructive role played by a BW laboratory in containing the virus. But we cannot blind ourselves to the knowledge that biological warfare now has one more potential weapon in its repertoire. Furthermore, a great deal of scientific ingenuity is dedicated to "improving" such agents, the most suicidal of human enterprises today.

Marburgvirus is but one example of the evils of nature that are our real enemies in the living world. It is very unlikely to discriminate between Democrat or Communist or Maoist. And as human society is now organized, our encounters with such threats will not for long be just near misses.

AIDS

THE ROCKEFELLER UNIVERSITY
1230 YORK AVENUE NEW YORK, NY 10021

December 10, 1986

JOSHUA LEDERBERG
PRESIDENT

Mr. Andrew Marshall
Office of Net Assessment
The Pentagon
Washington, D.C. 20301

Dear Andy:

Your letter of the 4th and its enclosure from Gene Durbin crossed a couple'things I just sent you about Aids, mainly the ad for the NAS publications.

I think the latter would bring you up-to-date on the main lines of present knowledge and if you have the time I would urge you to go through them. If that is too time consuming I think you might easily be able to get a briefing from some of the principals who put those reports together or some other group from the IOM.

I appreciated the chance to read Gene Durbin's comment; I was not really able to decipher too much of what he had handwritten. I wonder if your secretary would be able to transcribe those (more readily from your original) into type.

By and large I couldn't agree more with what Dr. Durbin has to say! I have been viewed as an alarmist on these matters -- the reaction to the concerns that I wrote about 25 and 20 years ago was a dull thud. The same happened again in 1975 at the Asilomar Conference on recombinant DNA when I tried to urge that the risks of not proceeding with that research were far greater than the potential hazardous by-products from well regulated laboratories.

The IOM reports are if anything shaded on the conservative side in their estimate of the situation. This was quite deliberate since even that presentation is sufficiently alarming and it is very difficult to know what to advocate, that would be furthered by enhancing the alarm even more. Both Baltimore and Temin are quite vehement in print, and personally that sexual transmission is all there is to worry about; the difference between Africa and the U.S. they would put down to unstated differences in sexual behavior. I am not at all confident of that; but at the moment there is no concrete evidence (happy to

say) of methods of transmission other than sexual contact and needle inoculation. However those are bad enough! They tend to pooh pooh my further concern that even if this is the prevalent mode of transmission now we have no assurance that the virus will not continue to evolve still further: it is presently in a very unstable stage of its recent evolution.

My main answer to Drubin's very last paragraph (#9) is that we don't have to invoke special environmental factors: the behavioral ones are quite sufficient and the virus has been evolving during the last 20 or 30 years accompanying its breakout from Central Africa, presumably from an animal reservoir.

There is no reason to believe that AIDS is the last word in what nature has in store for us. It is particularly insidious because of the very long latent period, and the fact that it attacks the immune system in such a way as to add further problematics to the possibility of the development of a vaccine. There is still a long shot that a vaccine can be effectively developed, presumably to act in conjunction with various forms of chemotherapy which are now extremely primitive when applied to viruses. But there would remain the enormous problem of testing such a vaccine to validate its efficacy. Certainly this is a problem far beyond the reach of the private sector, and, at the very least, government has to insure the liabilities that the private sector pharmaceutical industry would face in attempts at further development in this field. The vaccine hazard reimbursement bill that the President recently signed (with the utmost reluctance!) is at least a step in the right direction, although it would not in its present form apply to an AIDS vaccine.

Yes, there certainly does need to be a mobilization! The IOM committee recommendations that a national commission be established to look into all the social, political ramifications,as well as the strictly medical ones is a very sound one. Better that it not be centered on the DoD's special security concerns.

Just in the last week, in fact as I may have mentioned to you the same morning I saw you at DIAC, I was able to persuade my colleagues at IOM that we should be undertaking anticipatory studies to see what else might be on the horizon by way of these kinds of pandemic threat -- including some of the ones

Medical Science, Infectious Disease, and the Unity of Humankind

The ravaging epidemic of acquired immunodeficiency syndrome has shocked the world. It is still not comprehended widely that it is a natural, almost predictable, phenomenon. We will face similar catastrophes again, and will be ever more confounded in dealing with them, if we do not come to grips with the realities of the place of our species in nature. A large measure of humanistic progress is dedicated to the subordination of human nature to our ideals of individual perfectability and autonomy. Human intelligence, culture, and technology have left all other plant and animal species out of the competition. We also may legislate human behavior. But we have too many illusions that we can, by writ, govern the remaining vital kingdoms, the microbes, that remain our competitors of last resort for dominion of the planet. The bacteria and viruses know nothing of national sovereignties. In that natural evolutionary competition, there is no guarantee that we will find ourselves the survivor.

Some of the great successes of medical science, including the "miracle drugs," the antibiotics of the 1940s, have inculcated premature complacency on the part of the broader culture. Most people today are grossly overoptimistic with respect to the means we have available to forfend global epidemics comparable with the Black Death of the 14th century (or on a lesser scale the influenza of 1918), which took a toll of millions of lives.

Visualize human life on this planet as mirrored in the microcosm of a culture of bacteria; a laboratory test tube can hold ten billion cells, twice the human population of the globe. More than 70 years ago, Frederick William Twort and Felix d'Herelle discovered that bacteria have their own virus parasites, the bacteriophages. It is not unusual to observe a thriving bacterial population of a billion cells undergo a dramatic wipeout, a massive lysis, a sudden clearing of the broth following a spontaneous mutation that extends the host range of a single virus particle. A hundred billion virus particles will succeed the bacteria; but their own fate now is problematic, as they will have exhausted their prey (within that test tube). Perhaps there are a few bacterial survivors: mutant bacteria that now resist the mutant virus. If so, these can repopulate the test tube until perhaps a second round, a mutant-mutant virus, appears.

Such processes are not unique to the test tube. The time scale, the numerical odds, will be different. The fundamental biologic principles are the same.

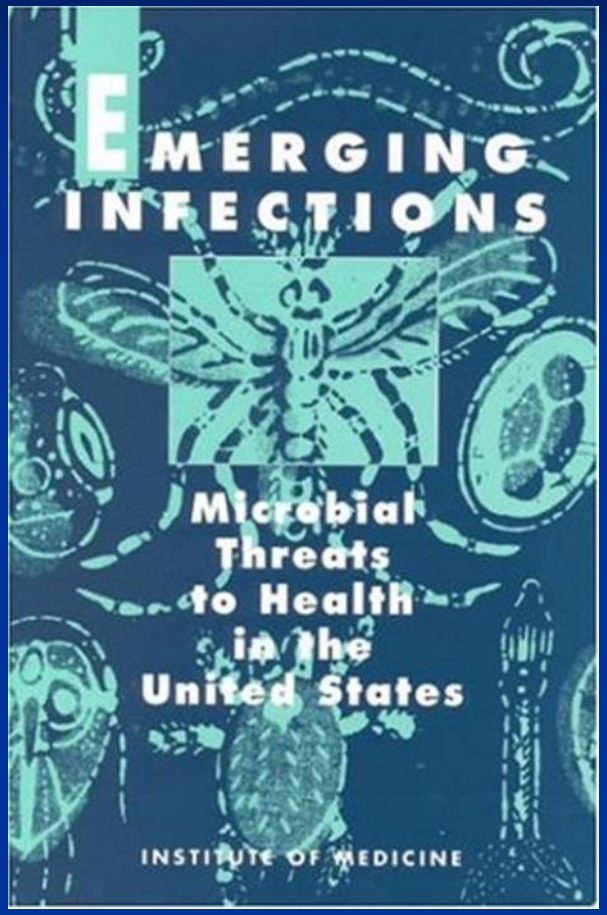
Humans are more dispersed over the planetary surface than are the "bugs" in a glass tube; there are more diverse sanctuaries, and we have somewhat fewer opportunities to infect one another. The culture medium in the test tube is more hospitable to virus transmission than is the space between people (with the exceptions of sexual contact and transfusion). The ozone shield still lets through enough solar ultraviolet light to hinder aerosol transmission, and most viruses are fairly vulnerable to desiccation in dry air. The unbroken skin is an excellent barrier to infection; the mucous membranes of the respiratory tract are much less so. Our immune defenses are a wonderfully intricate legacy of our own evolutionary history. This enables machinery for producing an indefinite panoply of antibodies, some one of which is (we may hope) a specific match to the antigenic challenge of a particular invading parasite.[1] In the normal, immune-competent individual, each incipient infection is a mortal race between the penetration and proliferation of the virus within the body and the evolution and expansion of antibodies that may be specific for that infection. Previous vaccination or infection with a related virus will facilitate an early immune response. This in turn provides selective pressure on the virus populations, encouraging the emergence of antigenic variants. We see this most dramatically in the influenza pandemics, and every few years we need to disseminate fresh vaccines to cope with the current generation of the flu virus.

Many defense mechanisms, inherent in our evolved biologic capabilities, thus mitigate the pandemic viral threat. Mitigation also is built into the evolution of the virus: it is a Pyrrhic victory for a virus to eradicate its host! This may have happened historically, but then both the vanquished host and the victorious parasite will have disappeared. Even the death of the single infected individual is relatively disadvantageous, in the long run, to the virus compared with a sustained infection that leaves a carrier free to spread the virus to as many contacts as possible. From the perspective of the virus, the ideal would be a nearly symptomless infection in which the

From the Office of the President, The Rockefeller University, New York. Dr Lederberg won the Nobel prize in physiology and medicine in 1958. This article was adapted from a presentation at a conference of Nobel laureates sponsored by François Mitterand and Elie Wiesel, Paris, January 1988.

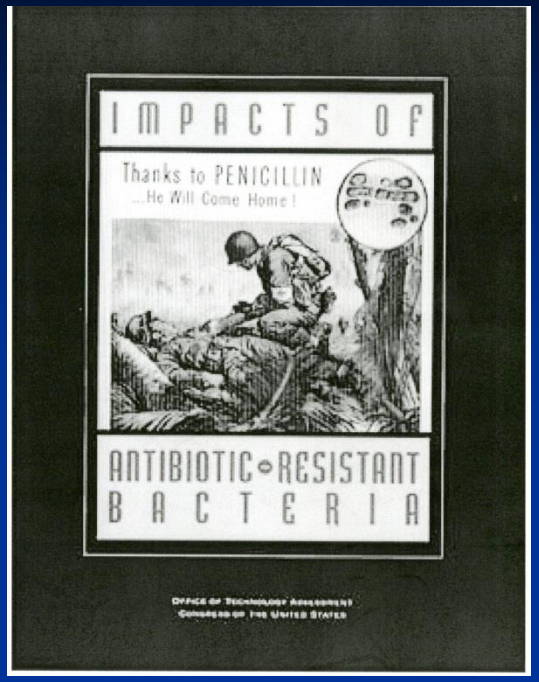
Reprint requests to Office of the President, The Rockefeller University, 1230 York Ave, New York, NY 10021-6399.

JAMA 260 (1988): 684-685

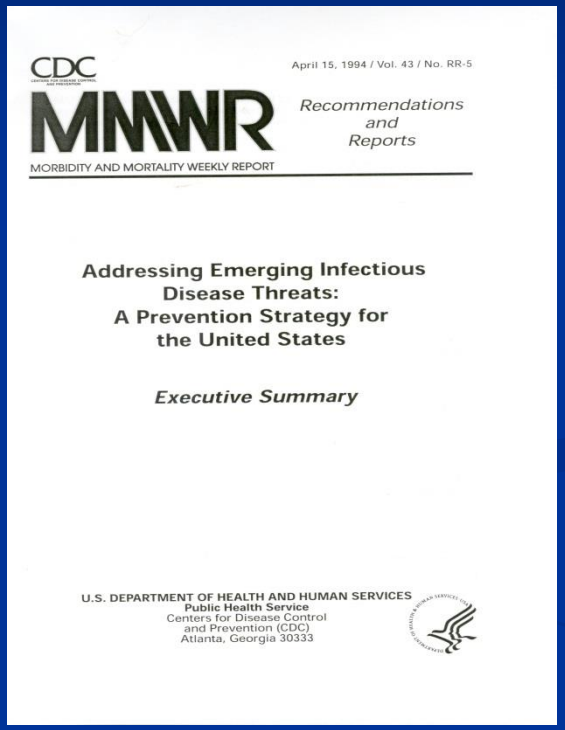


"Clinicians, the research and development community, and the U.S. government … introduce measures to ensure the availability and usefulness of antimicrobials and to prevent the emergence of resistance."

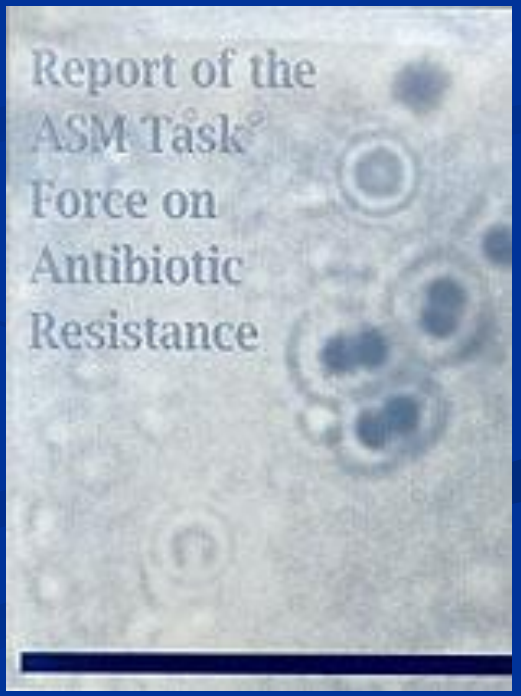
1992



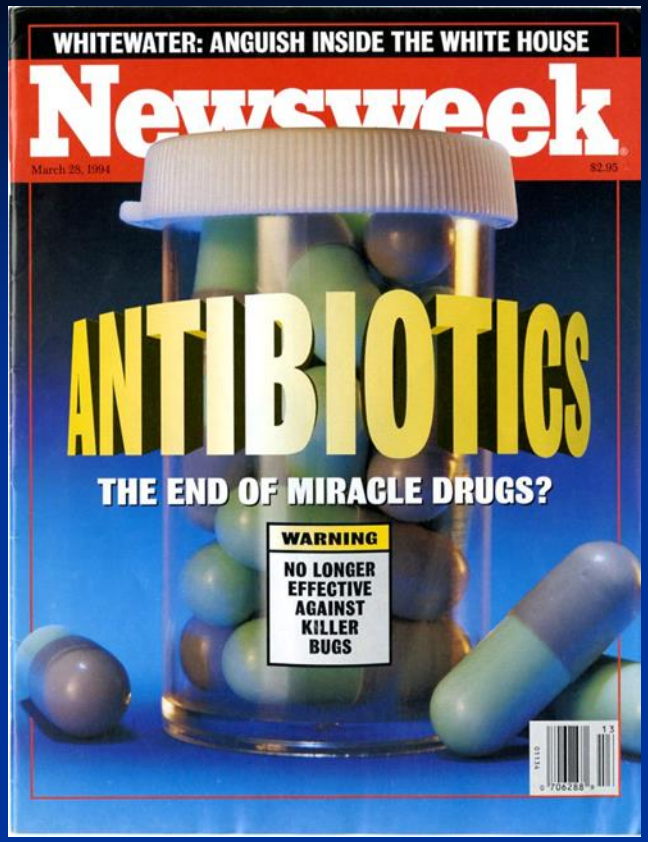
Office of Technology Assessment, 1995



Centers for Disease Control, 1994



American Society of Microbiology, 1995



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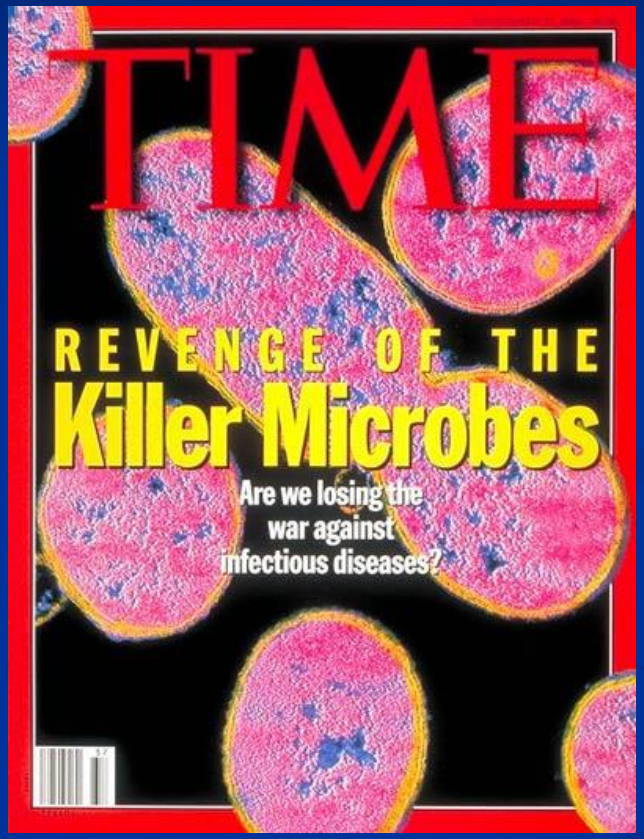

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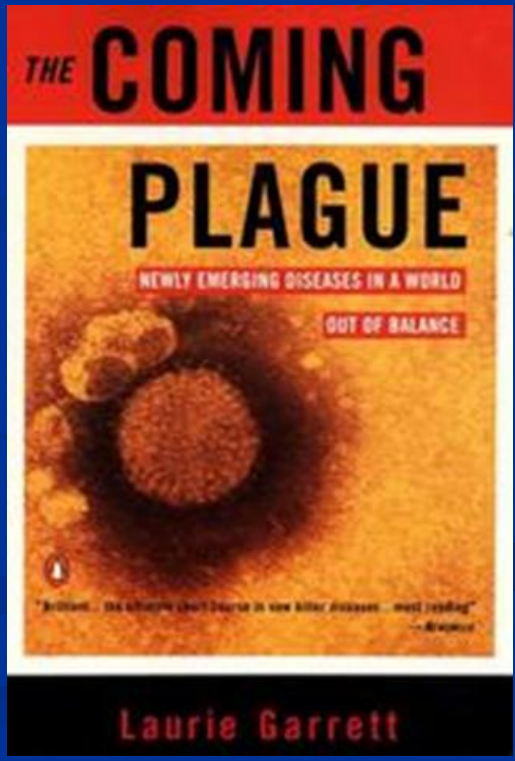
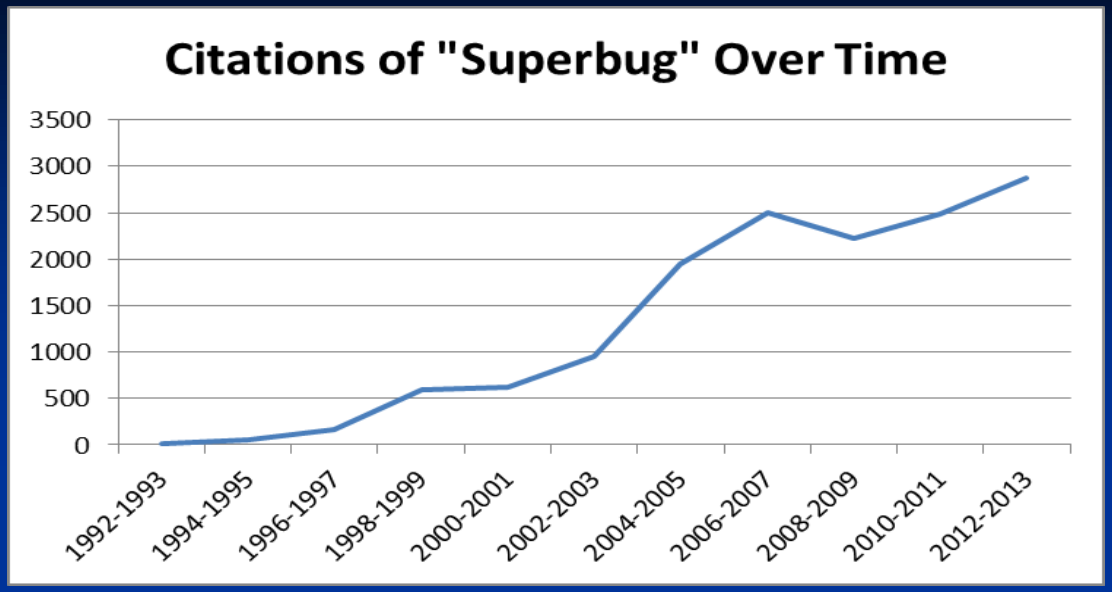
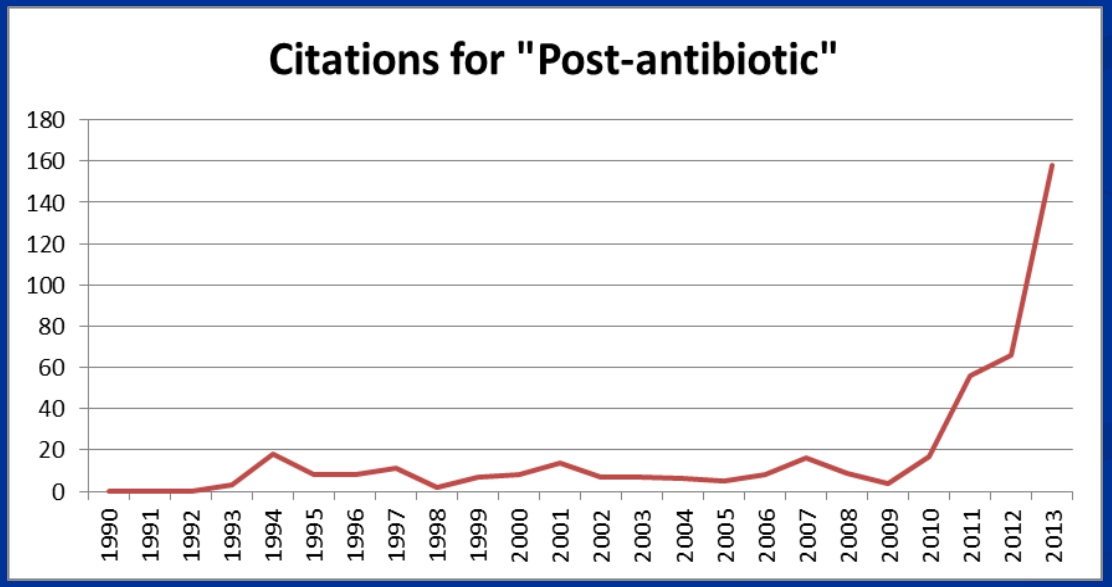
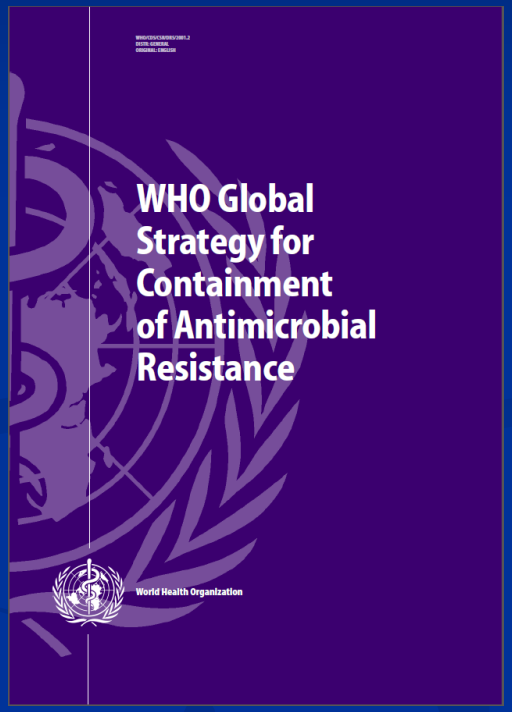


The Coming Plague (New York: Farrar, Straus &Giroux, 1994)







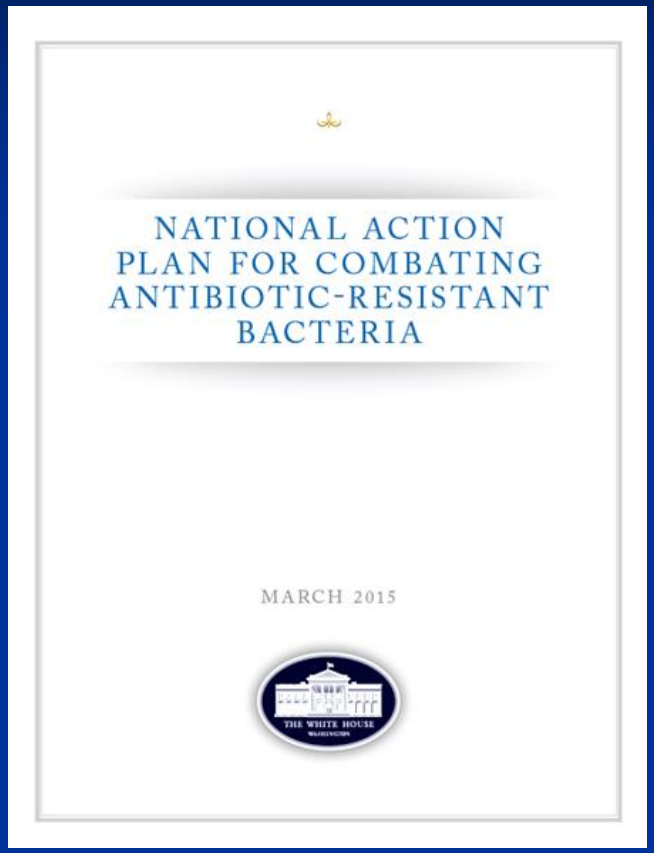
2001

Derived from LexisNexis Academic searches; see *The Antibiotic Era*, p. 177, for details

A Fifth Era (?), 2013-present

"Antimicrobial resistance is a ticking time bomb not only for the UK but also for the world. We need to work with everyone to ensure the apocalyptic scenario of widespread antimicrobial resistance does not become a reality. This is a threat arguably as important as climate change for the world."

Dame Sally Davies,
Chief Medical Officer for England, (first published online in 2013)


NATIONAL ACTION
PLAN FOR COMBATING
ANTIBIOTIC-RESISTANT
BACTERIA
MARCH 2015
THE WHITE HOUSE


GLOBAL ACTION PLAN
ON ANTIMICROBIAL
RESISTANCE
World Health
Organization

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY:
FINAL REPORT AND RECOMMENDATIONS

THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAIRED BY JIM O'NEILL

MAY 2016

Public Disclosure Authorized

Public Disclosure Authorized

Public Disclosure Authorized

Final Report

DRUG-RESISTANT INFECTIONS

A Threat to Our Economic Future

March 2017

WORLD BANK GROUP

GENERAL ASSEMBLY OF THE UNITED NATIONS

President of the 71st session

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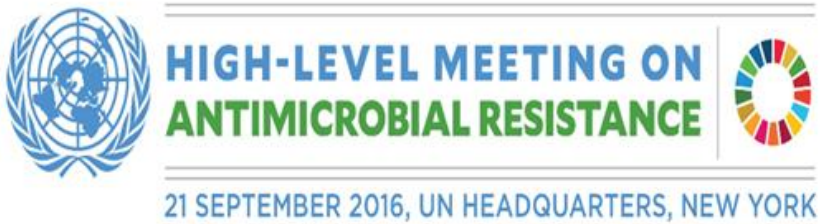
« All Events

High-level Meeting on Antimicrobial Resistance

September 21 @ 10:00 am - 6:00 pm



On 21 September 2016, the President of the UN General Assembly convenes an one-day high-level meeting at the UN Headquarters in New York on "Antimicrobial Resistance", with the participation of Member States, non-governmental organizations, civil society, the private sector and academic institutions, in order to provide input.

The primary objective of the meeting is to summon and maintain strong national, regional and international political commitment in addressing antimicrobial resistance comprehensively and multi-sectorally, and to increase and improve awareness of antimicrobial resistance.

Proposed Measures to Forestall the "Post-Antibiotic Era"

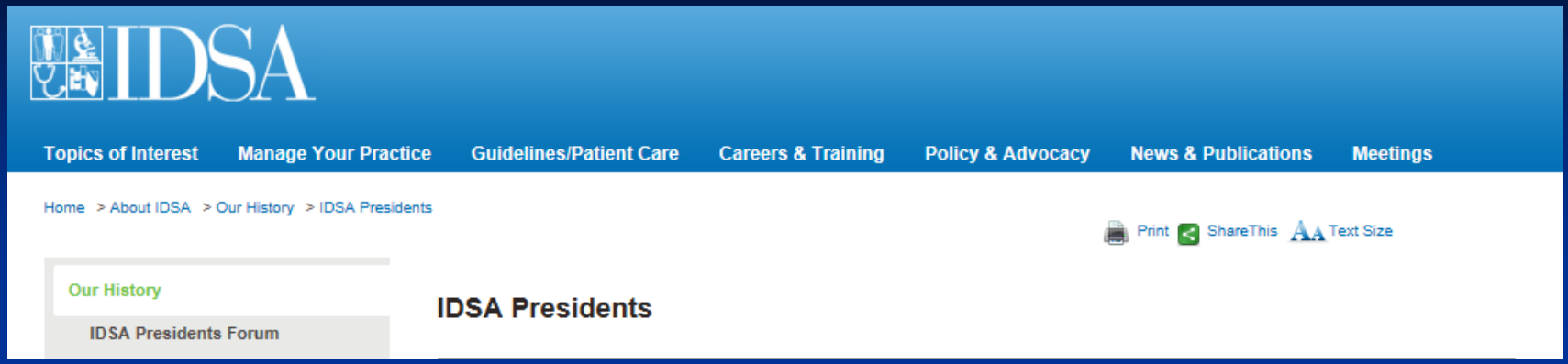
I. Improved Surveillance/Assessment of Extent of Usage

II. Decreased Demand (especially inappropriate)

- Vaccination and improved sanitation and infection control
- Public education
- Antibiotic stewardship and standardization of prescribing
- Improved diagnostics to undergird rational prescribing
- Decreased usage in agribusiness and veterinary medicine

III. Increased Supply

- Innovation funds (early stage R&D support)
- Ease of market entry (21st Century Cures … WWMFD?)



1974	George Gee Jackson, MD, FIDSA
1973	Leighton E. Cluff, MD, FIDSA
1972	Gordon Meiklejohn, MD, FIDSA
1971	Robert Austrian, MD, FIDSA
1970	Edward H. Kass, MD, PhD, FIDSA
1969	Albert B. Sabin, MD, FIDSA
1968	Walsh McDermott, MD, FIDSA
1967	Charles H. Rammelkamp, MD, FIDSA
1966	Harry F. Dowling, MD, FIDSA
1965	John F. Enders, PhD, FIDSA
1964	Maxwell Finland, MD, FIDSA

Source: IDSA website

Bad Bugs, No Drugs

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Brews

IDSA
Infectious Diseases Society of America

July 2004

Limited Population Antibacterial Drug (LPAD) Approval Mechanism

Background: The Need for a New FDA Approval Pathway for High-Priority Antibiotics

As the number of patients succumbing to antibiotic-resistant infections rises, the number of new antibiotics in development has plummeted. These findings underscore the need for antibiotic incentives and a feasible approval pathway to advance research and development (R&D) of desperately needed new antibiotics. FDA has an essential role to play in ensuring that Americans have access to safe and effective drugs. But, in so doing, the agency must ensure that the risks associated with approving new products are appropriately balanced against the products' benefits to patients and to society. To date, when it comes to antibiotics, and particularly antibiotics needed to treat patients with the most serious bacterial infections, FDA's risk-benefit equation has been out of balance. The U.S. regulatory environment is the primary reason that the few pharmaceutical companies still investing in antibiotic R&D report they plan to focus future efforts on markets outside of the United States.

The LPAD Approval Mechanism

The LPAD approval mechanism would provide an important new approval pathway for antibacterial drugs that treat patients with the most serious infections where there exists an unmet medical need (i.e., where insufficient satisfactory therapeutic options exist). It is not feasible for antibacterial drugs that treat serious infections due to highly resistant bacterial pathogens to be developed using traditional, large scale clinical trials due to the limited numbers of patients in which such serious infections occur. Instead, under the LPAD mechanism, a drug's safety and effectiveness would be studied in substantially smaller, more rapid, and less expensive clinical trials—much like the Orphan Drug (OD) Program permits for other rare diseases. LPAD products then would be narrowly indicated for use in small, well-defined populations of patients for whom the drugs' benefits have been shown to outweigh their risks. For patients with serious infections and insufficient therapeutic options, a greater degree of uncertainty about overall risk associated with a drug can be tolerated. The LPAD mechanism will not be used to approve antibacterial products that treat more common infections or where sufficient alternative therapeutic options exist.

The LPAD designation, a description of the indicated population, the rationale for limiting use, and an LPAD logo (similar to the logo pictured above) would appear in LPAD products' labeling. Through this information, FDA would be providing notice to the health care community and payors that these products carry less precise estimates of risk and, as a result, the drugs' marketing and use should be limited to the indicated population. LPAD products' limited use also would help slow the rate at which resistance to these drugs develops—an important goal of the medical, public health, and patient communities. Of critical importance, the LPAD mechanism ensures that clinical decision-making remains in physicians' hands. FDA will have no role in regulating use of approved products within the practice of medicine. However, FDA will be able to monitor LPAD products' safe use through its existing Sentinel System.

Dr. Janet Woodcock, director, FDA's Center for Drug Evaluation and Research, has stated that two companies have expressed interest in pursuing the LPAD mechanism, if the pathway is established. Woodcock also said the LPAD mechanism provides a potential way forward for companies to pursue urgently needed antibacterial drugs. IDSA knows at least seven companies with products that would fit under the LPAD mechanism and help the patients who desperately need access to these drugs.

Antibiotics are typically priced far below their true value to society. As with OD designations, an LPAD designation is expected to increase the price of these drugs, compared with traditionally approved antibiotics, making investment in LPAD antibiotics more attractive to pharmaceutical companies. The drugs' higher price, in turn, will encourage payors, the health care community and providers to play a more active role ensuring LPADs are used as indicated, which will help preserve the drugs' effectiveness.
Finally, the LPAD designation could be temporary or permanent. If the drug sponsor later went through a traditional study route for an additional broad indication, the LPAD designation would be removed.

TAM15060 S.L.C.

114TH CONGRESS
1ST SESSION

S. _____

To create a limited population pathway for approval of certain antibacterial drugs.

IN THE SENATE OF THE UNITED STATES

Mr. HATCH (for himself and Mr. BENNET) introduced the following bill; which was read twice and referred to the Committee on _____

A BILL

To create a limited population pathway for approval of certain antibacterial drugs.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Promise for Antibiotics and Therapeutics for Health Act" or the "PATH Act".

SEC. 2. LIMITED POPULATION PATHWAY FOR ANTIBACTERIAL DRUGS.

Section 506 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356) is amended—

thebmj

BMJ 2015;350:h1453 doi: 10.1136/bmj.h1453 (Published 25 March 2015)

FEATURE

ANTIBIOTICS

Speeding new antibiotics to market: a fake fix?

Antibiotic development may finally be picking up pace, with 11 new drugs approved in the past decade, four in 2014 alone, with the help of new legislation. But in this first installment of a series on antibiotics, **Peter Doshi** asks why authorities are approving drugs with little evidence they do anything to tackle the problem of antimicrobial resistance

Peter Doshi *associate editor, The BMJ*

US president Barack Obama has called the problem of antimicrobial resistance "a serious threat to public health and the economy."[1] In the UK, Sally Davies, chief medical officer for England, declared the problem "as important as global warming,"[2] and a "ticking time-bomb"[3] while the prime minister, David Cameron, says: "we are in danger of going back to the dark ages of medicine."[4]

Over the past few decades industry has turned its eyes towards the more profitable markets in chronic diseases—the blockbuster cardiovascular and psychiatric drugs, for example—and attention on much needed antibiotics has waned. This has resulted in fewer antibiotics able to keep up with the march of evolutionary resistance. Incentives for drug development have therefore become a key focus of efforts to tackle antimicrobial resistance, alongside improved infection control and antibiotic stewardship.

The Food and Drug Administration now offers a series of marketing incentives for new antibiotics. Backed by a law passed by Congress in 2012, 61 chemical entities have been granted "qualified infectious disease product" (QIDP) status, promising manufacturers accelerated review of new drug applications and five additional years of marketing exclusivity. Another bill introduced into the US Congress this year aims to substantially lower the requirements for FDA approval for certain new antibiotics, including the need for phase III trials, by allowing preclinical and pharmacokinetic data to serve as "confirmatory evidence" underpinning approval.[5]

So are the antibiotics approved under this new relaxed regime fulfilling the vision to treat infections that were previously untreatable because of resistant organisms?

Rising tide of new antibiotics—but are they better?

Four QIDPs were approved in 2014—dalbavancin, tedizolid, oritavancin, and ceftolozane/tazobactam, and a fifth, ceftazidime-avibactam, was approved in February. They promise to be the first of many.

The 2012 legislation that made this fast tracking possible—the Generating Antibiotic Incentives Now Act (GAIN)—says that to qualify as a QIDP, the antibiotics need to treat "serious or life-threatening infections, including those caused by an antibacterial or antifungal resistant pathogen." Once granted, QIDP designation helps speed drug approval by placing the drug in either the "fast track" or the "priority review" regulatory pathway.

Ordinarily, drugs qualify for fast track when, in the FDA's words, "data demonstrate the potential [of the drug] to address an unmet medical need."[6] Curiously, however, three of the five new antibiotics were approved to treat the same indication—acute bacterial skin and skin structure infections. Over 30 other drugs are already approved for these infections, of which at least six are approved for methicillin resistant *Staphylococcus aureus* (MRSA).

"There are no criteria requiring these products [dalbavancin, tedizolid, and oritavancin] to address an unmet medical need," FDA spokesperson Stephanie Yao said in an interview.

Yet when I asked the FDA why new options for acute skin infections were important given the many existing approved therapies, the agency invoked the concept of unmet medical need: "New antibacterial drugs are critically needed to address current unmet medical needs and to ensure availability of antibacterial drug options to treat patients in the future."

According to the FDA, a drug which both "treats a serious condition" and also, "if approved would provide a significant improvement in safety or effectiveness" qualifies for the other expedited approval mechanism, priority review.[6] All five newly approved antibiotics received it, but QIDP designated drugs need not meet traditional criteria to qualify.

"A QIDP product is an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections and does not have to show added benefit in terms of efficacy," the FDA told *The BMJ*. The implication is that "improvement in safety or effectiveness" does not apply to QIDP antibiotics.

pdoshi@bmj.com

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

JUNE 25, 2015

The 21st Century Cures Act — Will It Take Us Back in Time?

Jerry Avorn, M.D., and Aaron S. Kesselheim, M.D., J.D., M.P.H.

In May 2015, the 21st Century Cures Act was introduced in the U.S. House of Representatives, with the goal of promoting the development and speeding the approval of new drugs and devices.[1] Championed by the pharmaceutical, biotechnology, and device industries, the bill was approved unanimously (51 to 0) in committee and continues to be debated. If enacted into law, some of its provisions could have a profound effect on what is known about the safety and efficacy of medical products, as well as which ones become available for use.

Some aspects of the bill could indeed enhance the development of and access to new drugs. The legislation calls for annual increases in the stagnating budget for the National Institutes of Health (NIH) amounting to about 3% per year for 5 years when adjusted for inflation. It would also provide an additional $2 billion per year for 5 years to create an "NIH Innovation Fund." Together, this support would help counteract the effects of sequestration and budget cuts that have reduced the purchasing power of the NIH to its lowest level in years. Given the crucial role that NIH-funded research plays in generating the findings on which so many new drugs are based,[2] this boost would be a welcome development. Another useful provision could make deidentified data from NIH-funded clinical trials more available to researchers.

Other proposed changes could lead to less salutary outcomes for patients and the health care system. An underlying premise of the bill is the need to accelerate approval for new products, but this process is already quite efficient. A third of new drugs are currently approved on the basis of a single pivotal trial; the median size for all pivotal trials is just 760 patients. More than two thirds of new drugs are approved on the basis of studies lasting 6 months or less[3] — a potential problem for medications designed to be taken for a lifetime. Once the Food and Drug Administration (FDA) starts its review, it approves new medications about as quickly as any regulatory agency in the world, evaluating nearly all new drug applications within 6 to 10 months, an impressive turnaround for such complex assessments.

Regulating Antibiotics in an Era of Resistance: The Historical Basis and Continued Need for Adequate and Well-Controlled Investigations

Scott H. Podolsky, MD; and John H. Powers III, MD

[+] Article, Author, and Disclosure Information

Ann Intern Med. 2015;163(5):386-388. doi:10.7326/M15-0802

This article was published online first at *www.annals.org* on 14 July 2015.

Two bills introduced in Congress (the Promise for Antibiotics and Therapeutics for Health Act and the Antibiotic Development to Advance Patient Treatment Act of 2013 in the 21st Century Cures Act) propose changes in the regulatory approval of new antibiotics in the context of attempts to reengage industry amidst fears of a postantibiotic future. Despite anti-infectives having among the shortest development times and highest approval rates among therapeutic classes (1–3), some propose that the requirements of adequate and well-controlled trials make the study of new antibiotics infeasible (4). To address perceived hurdles, these bills propose a regulatory pathway in poorly defined "limited populations" without requiring demonstrated benefits in populations with resistant disease. Studies would be done in patients with effective options rather than those with unmet medical needs, allowing approval even with inferior effectiveness in the population studied. No requirement for diagnostics means that the drugs may be prescribed empirically outside the limited population. The bills would alter the standard of approval from substantial evidence to "sufficient evidence" derived from "small clinical data sets" and would consider preclinical data, animal models, and pharmacologic data to be "confirmatory evidence." In the setting of such proposals, historical reflection is in order.

Antibiotics were the leading example of post–World War II "wonder drugs," dramatically rebranding medicine. They were the most lucrative segment of the pharmaceutical industry and transformed such companies as Pfizer and Parke-Davis. Yet, despite the advent of penicillin and broad-spectrum antibiotics, by the early 1950s staphylococcal resistance led to the perceived need for an arms race to keep up with life-threatening diseases caused by resistant organisms (5).

By the mid-1950s, pharmaceutical companies marketed antibiotic combinations, predicated on in vitro synergy, as solutions to resistant organisms. However, leading infectious disease researchers, including Maxwell Finland, Harry Dowling, and Ernest Jawetz, found them to be no more effective than their components in treating human disease; strain-dependent in their action; and, hence, not amenable to prepackaged formulations. Despite these observations, the drugs were widely promoted and used in what Finland and Dowling perceived as an evidentiary vacuum. At the time, the U.S. Food and Drug Administration (FDA) could only formally adjudicate drug safety (not efficacy). To Finland and Dowling, the widespread marketing and uptake of these antibiotics, based on what they termed "testimonials" (case series supported by in vitro data), portended a future of style over substance that threatened the very future of rational therapeutics (5).

Conclusion

"What is the future of antibiotics? Antibiotics are here to stay. Others, less toxic and more active … will be found. Costs will be reduced. Side effects will be either eliminated or controlled. Physicians will have well equipped laboratories at their disposal to evaluate each antibiotic and determine at once the particular antibiotic required for the treatment of a specific disease. Self medication will be reduced to a minimum. Government control of antibiotics will be tightened, so as to render antibiotics safer, more useful, and less expensive. The antibiotic era will accomplish what nature has intended it to be: Man's control over infectious diseases and epidemics that have plagued mankind since prehistoric times."

Selman A. Waksman, 1963

From the Selman Waksman papers, Rutgers University Libraries

"What is the future of antibiotics? Antibiotics are here to stay. Others, less toxic and more active … will be found. Costs will be reduced. Side effects will be either eliminated or controlled. Physicians will have well equipped laboratories at their disposal to evaluate each antibiotic and determine at once the particular antibiotic required for the treatment of a specific disease. Self medication will be reduced to a minimum. Government control of antibiotics will be tightened, so as to render antibiotics safer, more useful, and less expensive. The antibiotic era will accomplish what nature has intended it to be: Man's control over infectious diseases and epidemics that have plagued mankind since prehistoric times."

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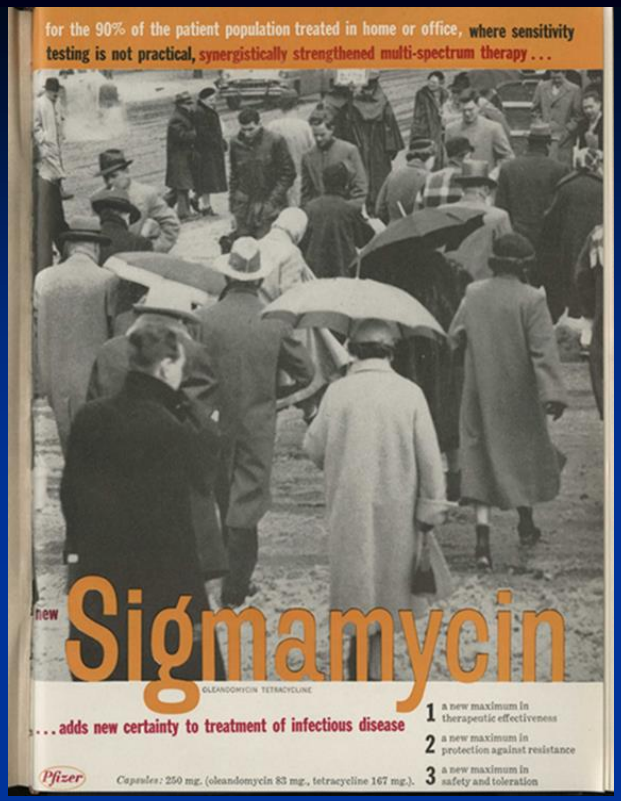
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new
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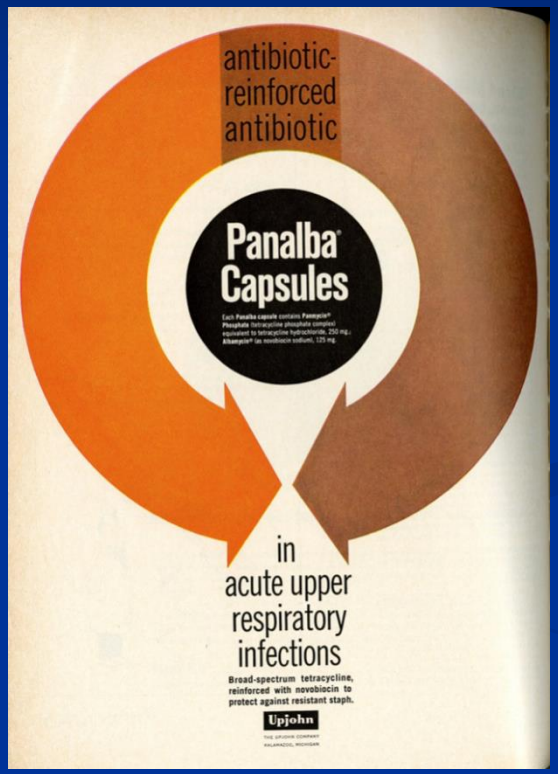
OLEANDOMYCIN TETRACYCLINE
. . . adds new certainty to treatment of infectious disease
1 a new maximum in therapeutic effectiveness
2 a new maximum in protection against resistance
3 a new maximum in safety and toleration
Pfizer
Capsules: 250 mg. (oleandomycin 83 mg., tetracycline 167 mg.).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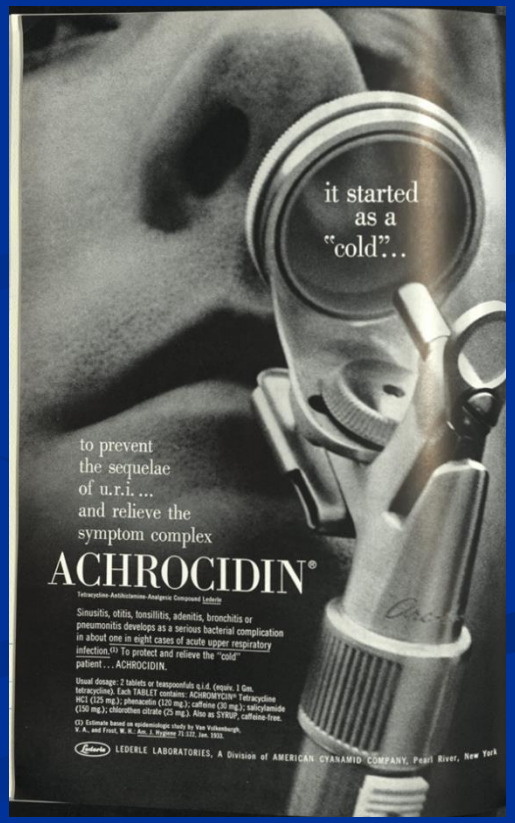
it started
as a
"cold"...
to prevent
the sequelae
of u.r.i. ...
and relieve the
symptom complex
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Sinusitis, otitis, tonsillitis, adenitis, bronchitis or pneumonitis develops as a serious bacterial complication in about one in eight cases of acute upper respiratory infection.(1) To protect and relieve the "cold" patient . . . ACHROCIDIN.
Usual dosage: 2 tablets or teaspoonfuls q.i.d. (equiv. 1 Gm. tetracycline). Each TABLET contains: ACHROMYCIN® Tetracycline HCl (125 mg.); phenacetin (120 mg.); caffeine (30 mg.); salicylamide (150 mg.); chlorothen citrate (25 mg.). Also as SYRUP, caffeine-free.
(1) Estimate based on epidemiologic study by Van Volkenburgh, V. A., and Frost, W. H.: Am. J. Hygiene 73:122, Jan. 1961.
Lederle LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

TASK FORCE ON PRESCRIPTION DRUGS

FINAL REPORT

February 7, 1969

Office of the Secretary

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Washington, D.C. 20201

CHAPTER 4

THE DRUG PRESCRIBERS[a]

In the modern use of drugs, important roles are played by the drug researcher, the manufacturer, the distributor, the pharmacist, and the official who carries the legal responsibility for drug safety, efficacy and quality. But the most strategic role is that of the physician who prescribes the drug.

It is the physician who has major responsibility for the welfare of the patient.

It is the physician who is constantly faced with an awesome assortment of competitive and often duplicative products.

It is the physician who is the target of a barrage of advice, information, guidance, and promotion from detail men, advertisements, medical articles, pamphlets, bulletins, and throw-away journals.

And it is the physician who—with or without adequate training and competent advice—must make the decision on which drug or drugs to prescribe.

On his decision may well depend the health or even the life of his patient. On it will depend, at least in part, the quality, cost and effectiveness of any drug insurance program, governmental or nongovernmental. And on it will depend the economic well-being of a drug company.

Rational Prescribing

The appropriate selection of a drug—the right drug for the right patient, in the right amounts at the right times[1]—is generally defined as rational prescribing, and any significant deviation is considered to be irrational prescribing.

Rational prescribing is obviously the result of judgments on many points—the safety and efficacy of the drug for the clinical problem at hand, the advantages or disadvantages of alternative forms of therapy, the most appropriate dosage form, the length and intensity of treatment, the possible side-effects or adverse reactions, and the possibility of drug interaction.[2]

To these may be added judgments concerning relative costs.

Rational prescribing is clearly a major goal for the welfare of patients. It is likewise a major goal for any drug insurance program. Here, emphasis has been placed not directly on achieving rational prescribing but rather on preventing some of the more serious or costly forms of irrational prescribing. Among the latter are these:

- The use of drugs without demonstrated efficacy.[3]
- The use of drugs with an inherent hazard not justified by the seriousness of the illness.[4]
- The use of drugs in excessive amounts, or for excessive periods of time, or inadequate amounts for inadequate periods.[5]
- The use of a costly duplicative or "me-too" product when an equally effective but less expensive drug is available.[6]
- The use of a costly combination product when equally effective but less expensive drugs are available individually.[7]
- The simultaneous use of two or more drugs without appropriate consideration of their possible interaction.[8]
- Multiple prescribing, by one or several physicians for the same patient, of drugs which may be unnecessary, cumulative, interacting, or needlessly expensive.[9]

We recognize that some patients may be receiving as many as 16 to 20 different drugs simultaneously, prescribed by either one or several different physicians,[10] and that often physicians may not be aware that their patients are receiving drugs prescribed by others.

We see no reason to believe that any or all of these types of irrational prescribing can be effectively prevented—or that rational prescribing can be effectively induced—merely by rules and regu-

[a] This chapter updates the material presented originally in the First and Second Interim Reports of the Task Force.

[1] Task Force on Prescription Drugs: "The Drug Prescribers," U.S. Government Printing Office, Washington, D.C., 1968, p. 3.

[2] *Ibid.*, pp. 4–5.

[3] *Ibid.*, pp. 3–4, 36–37.

[4] Goodman, Louis, *ibid.*, p. 4.

[5] Talalay, Paul, *ibid.*, p. 5.

[6] Task Force on Prescription Drugs: "The Drug Makers and the Drug Distributors," U.S. Government Printing Office, Washington, D.C., 1968, pp. 20–22.

[7] Kunin, Calvin M., cited in "The Drug Prescribers," *op. cit.*, p. 5.

[8] Goldenthal, Edwin I., *ibid.*, p. 5.

[9] Cluff, Leighton E., *ibid.*, p. 5.

[10] "The Drug Prescribers," *op. cit.*, p. 5.

ASIA PACIFIC

306 COMMENTS

'Superbugs' Kill India's Babies and Pose an Overseas Threat

By GARDINER HARRIS DEC. 3, 2014

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AMRAVATI, India — A deadly epidemic that could have global implications is quietly sweeping India, and among its many victims are tens of thousands of newborns dying because once-miraculous cures no longer work.

These infants are born with bacterial infections that are resistant to most known antibiotics, and more than 58,000 died last year as a result, a recent study found. While that is still a fraction of the nearly 800,000 newborns who die annually in India, Indian pediatricians say that the rising toll of resistant infections could soon swamp efforts to improve India's abysmal infant death rate. Nearly a third of the world's newborn deaths occur in India.

"Reducing newborn deaths in India is one of the most important public health priorities in the world, and this will require treating an increasing number of neonates who have sepsis and pneumonia," said Dr. Vinod Paul, chief of pediatrics at the All India Institute of Medical Sciences and the leader of the study. "But if resistant infections keep growing, that progress could slow, stop or even reverse itself. And that would be a disaster for not only India but the entire world."

A mother nursing her newborn at a hospital in Haryana, where almost every baby born in hospitals in recent years has been injected with antibiotics. Kuni Takahashi for The New York Times

Thank you

Jerry Avorn
Kathryn Baker
Anne Becker
Allan Brandt
Robert Bud
Daniel Carpenter
Iain Chalmers
Clare Chandler
Flurin Condreau
Arthur Daemmrich
Jack Eckert
Paul Farmer
Mark Finlay
Christoph Gradmann
Jeremy Greene
Robert Guidos
Greg Higby
Steven Hoffman
Thomas Huang
David Jones
Suzanne Junod
Ted Kaptchuk
Aaron Kesselheim
Claas Kirchhelle
Jerry Klein
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