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Statement

By

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Before the

Substance Abuse and Mental Health Services Administration

Center for Substance Abuse Treatment

Food and Drug Administration

November 1, 1999

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Chairmen and Members of the Interagency Panel, I am pleased to present the views of the American Methadone Treatment Association regarding the development of a new methadone evaluation system based on the principles of an accreditation model.

The American Methadone Treatment Association represents 643 methadone programs throughout the United States providing methadone treatment services for 151,329 patients through the organizing vehicle of State Methadone Provider Associations.

The Association has continually demonstrated its commitment to improve treatment practices through the development of national conferences, regionalized symposia and the publication of treatment standards and guidelines.

Support for an Accreditation Based System

The Association's support for the development of standardized outcome measures in evaluating the efficacy of methadone treatment can be traced back to the development of the State Methadone Treatment Guidelines. These Guidelines were developed following the publication of several critical reports on the effectiveness of methadone treatment in the United States.

The Association's support for accreditation in evaluating the effectiveness of methadone treatment is rooted in the fact that a major segment of the healthcare system in the United States is being reviewed through such accreditation standards. We believe that accrediting methadone treatment will offer the potential of embracing methadone treatment as part of mainstream medicine in the United States. We understand that the elements of such accreditation standards will draw upon the principles of the aforementioned State Methadone Treatment Guidelines, fulfilling the promise of ensuring that patients will be able to access a reliable standard of care, regardless of the size and location of a particular program or state policy.

The Association supported the implementation of the accreditation pilot project to incorporate 180 programs in the study, which is taking place in fifteen states. We are hopeful that the pilot will yield valuable information to guide federal agencies in developing a Final Rule, which will lead to the broad implementation of an accreditation system for methadone treatment throughout the United States.

It is critical that credible data are used to develop a blueprint to execute such a major transition in regulatory oversight. We anticipate that this

transition will be more costly than the federal agencies have anticipated, based on the data contained in the federal register notice of July 22, 1999. We have attached reports from methadone program administrators in different states, underscoring such concerns, especially as they relate to the indirect costs of implementing accreditation standards in their respective treatment programs.

The Association is also concerned about the duplication of regulatory oversight, which creates conflict and incurs significant expense. It is hoped that one uniform standard will be adopted and implemented in accordance with recommendations from the Institute of Medicine and federal agencies. The following comments detail the Association's response to the Notice for Proposed Rule Making.

Analysis of Impacts

The NPRM provides a baseline description of the treatment system. It indicates that the FDA has approved 869 methadone treatment programs as of early 1997, which encompass outpatient maintenance programs exclusively. Our Association recently conducted a survey of methadone treatment programs in the 42 states and the District of Columbia and found that 785 treatment programs were in existence. We realize that this number did not incorporate a number of VA methadone treatment programs, which would have increased the total.

The NPRM also indicated that the Secretary "estimates the total census of patients in opioid treatment to be approximately 125,000." The Association's 1998 survey data indicated that approximately 179,000 people were in treatment throughout the United States.

The Association has reviewed federal agency reports, indicating that more than 800,000 individuals are dependent on opiates throughout the United States (ONDCP – March, 1999). We understand that the intent of the Proposed Rule is also to increase access to care through the vehicle of accreditation.

It is certainly possible, that treatment will be made more available to people in need of care through the vehicle of accreditation, however, without an infusion of significant funds at the federal level, meaningful treatment expansion will not occur. Accreditation alone cannot be expected to increase access to care unless there is a commitment of funds to educate the public about the value of methadone treatment and to increase access to new treatment sites.

Costs of the Proposed Regulation

The NPRM discusses the cost of the proposed regulations. It presents information about the direct costs of becoming accredited in addition to indirect costs of improving program procedures to meet accreditation standards.

This section also amortizes the one time cost of accreditation over a three year period of time. This represents a contrivance since the program will incur accreditation costs immediately.

It appears that the direct cost of accrediting a methadone treatment program ranges from \$7,500.00 - \$11,000.00 (refer to Appendix A, which provides additional information).

A review of Appendix A indicates that a number of currently accredited methadone programs have incurred significant staff costs in preparing for accreditation surveys and implementing post survey improvements to be in compliance with accreditation standards. Unfortunately, all of the reporting programs were not able to accurately capture the indirect staff costs, which were incurred in preparing for accreditation surveys.

Three of the reporting states, which are listed in Appendix A, indicate significant indirect costs. Illustratively, the Missouri based methadone program reported a \$35,000.00 expenditure for staff time, computer upgrade and physical plant improvement. The Rhode Island program incurred expenses in the amount of \$26,916.00, including the development of an infectious control manual and the hiring of a mental health consultant. The Texas based program reported an indirect cost in the amount of \$45,000.00, which is related to the retention of a full time psychologist.

It is hoped that the fiscal data, which will result from the accreditation pilot study, will yield accurate information prior to the full-scale implementation of accreditation in methadone maintenance treatment.

Recommendation to Establish a Federal Fund

Our Association is urging the federal government to develop a multiyear, multipurpose fund to ensure that methadone treatment programs and patients will not be adversely affected by the implementation of accreditation standards, ultimately, decreasing access to care through program closure.

This fund may be developed on a needs based model, which would pay for the cost of the survey. The fund would also provide financial and technical support in implementing improvements as a result of the accreditation survey, which would include training of personnel, implementing new information management systems and executing physical plant improvements.

The Association recommends that the results of the pilot project be used as a basis in developing such a federal fund. If such a fund is not established, access to care will be affected as programs close under the weight of excessive fiscal burdens. Appendix A indicates that the indirect costs of implementing accreditation are considerable.

The Role of the FDA and the States

The Association conducted a survey of the State Methadone Authorities following the release of the Proposed Rule. The results of this survey are summarized in Appendix B. Six states have indicated that twenty-one treatment programs are currently in violation of FDA regulations. Ten states have reported that forty-five programs are in violation of current state regulations. Five states have indicated that five programs are in danger of closing. Twenty-nine states have indicated that 155 programs need programmatic technical assistance. Sixteen states have indicated that twenty-five programs need physical plant improvements. Twenty-one states rated 172 programs as excellent. Thirty states rated 209 programs as good. Twenty-five states have rated 145 programs as fair and eleven states rated 36 programs as poor.

The findings from the states are significant in providing direction to the federal government concerning the challenges of changing to accreditation based outcome oriented oversight. The federal agencies, which will be responsible for implementing accreditation standards, must be mindful of the challenges to the treatment system in executing such sweeping changes.

The role of the FDA must be clearly communicated to the states and to treatment programs during the accreditation pilot, providing guidance leading to the full-scale implementation of accreditation, once the results of the pilot have been fully evaluated.

Will the FDA continue to be involved in conducting “for cause” inspections of methadone treatment programs? If the FDA is expected to conduct such “for cause” inspections, has the Secretary developed a realistic budget to implement such a policy? How will the FDA determine if such “for cause” inspections are needed? How will the FDA work in conjunction with CSAT in conducting “for cause” inspections? How will

the FDA work in conjunction with State Methadone Authorities in conducting such inspections? Clearly, such questions are beyond the scope of our Association and have not been incorporated in the Notice for Proposed Rule Making.

Role of the States

Individual states have promulgated regulations, governing the practices of methadone programs in their respective jurisdictions. In certain states, such regulatory oversight has been executed to compensate for the dearth of FDA oversight. In other states, the specific interests of elected and appointed officials have been taken into account.

Recommendations to Work with the States in Developing a Uniform Accreditation System

The Association recommends that the federal agencies, which are responsible for implementing accreditation, work in conjunction with the State Authorities to maximize the use of one accreditation standard. We realize that several entities may be involved in conducting such accreditation reviews. We urge the federal government not to approve an excessive number of entities to be involved in conducting such accreditation, since it would run counter to the intent of developing a stable oversight mechanism. The greater number of entities, which would be involved in conducting accreditation surveys, will also produce greater variation in the standards of care.

The Association is hopeful that states will adopt accreditation body findings once it is determined that the accreditation surveys are responding to the needs of the states in ensuring that good quality care is being provided within the methadone treatment programs. We have been informed by a number of State Authorities that they would not be willing to adopt accreditation body findings in lieu of their own state inspections.

Recommendations for Office Based Methadone Treatment Practice

The NPRM discusses how federal opioid treatment standards might be “modified to accommodate office based treatment.” The Rule asks if a separate set of treatment standards should be included in the Rule for office based treatment.

The Association has recommended that methadone treatment be offered in office based medical practices through the vehicle of expanding access to “medical maintenance treatment”. These recommendations have been listed in Appendix C. These recommendations include criteria for

participating treatment programs, office based practitioners and patient referrals.

The Association believes that stable patients should be given treatment options, including a referral from the hub methadone treatment program to an office-based practice. Medical maintenance programs currently operate in New York State and Maryland. Research indicates that approximately seven percent (12,530) of the existing patient population (179,000) would be eligible for such medical maintenance treatment.

If the federal government agrees with the concept of expanding access to medical maintenance treatment, the Rule should be modified to allow such office based practitioners, which have established referral linkages from hub methadone treatment program sites, to keep such stable patients without meeting the burden of accreditation standards. Under this scenario, methadone treatment programs would meet the accreditation standards and the individual office based practice would not be required to offer the full range of comprehensive services, which are available at the OTP.

We understand that there is interest in providing access to treatment in office based practices with physicians treating a number of patients, who would be newly admitted without a referral from an existing OTP. Current regulations allow for physicians to be involved in such practices in areas where patients cannot get ready access to care. Our Association is not opposed to providing access to people in need of care under such circumstances.

Our Association does not support the policy of having physicians involved in treating newly admitted patients, which have not been referred through a hub referral site, where treatment is available at an OTP.

A number of critics have indicated that our Association's Medical Maintenance Criteria are rigid, citing international research and clinical practices. Our Association has received conflicting information about the success of such initiatives in Europe and Australia. Drs. John Caplehorn and Olaf Drummer published an article in the February 1, 1999 edition of the *Medical Journal of Australia*, titled "Mortality Associated with New South Wales Methadone Programs in 1994: Lives Lost and Saved". The article discussed how lives were saved in preventing heroin overdose deaths and also presented findings about methadone related deaths caused by accidental toxicity. (The article has been attached - Appendix D.)

"Methadone was detected in postmortem material from eighty-nine New South Wales coronial cases in 1994. These cases comprised forty-one methadone maintenance patients (thirty-eight registered with the New

South Wales Health Department). . . .Of the thirty-eight New South Wales maintenance patients, thirteen died in the first two weeks after admission and twenty-five died later in treatment. We and the official pathologists concluded that twelve of the thirteen fatalities in the first two weeks of maintenance and six of the twenty-five deaths later in treatment were caused by accidental toxicity.”

The authors also cited two recent British studies, from Sheffield and Manchester, which “similarly identified significant numbers of deaths from iatrogenic methadone toxicity early in maintenance treatment. These problems also arose after the relaxation of admission criteria and during a period of rapid increase in the numbers of maintenance patients and the involvement of new, inexperienced prescribers.”

If the federal government were to certify individual physicians to provide treatment to newly admitted opiate dependent patients and develop a separate standard of care, a two tiered system would inevitably emerge. If the federal government has a plan to encourage physicians to treat newly admitted opiate dependent patients, independent of the existing OTP, then the same standard of care should be applied. Such individual program practitioners should be subject to the same accreditation standards as the existing OTP.

Recommendations for Accrediting Small OTPs

The Association has received a number of inquiries from small treatment programs in different states. They have expressed great concern about discontinuing their operations since they treat fewer than seventy-five patients at the program setting.

One of the reasons that the Association encouraged a large sample to be included in the accreditation pilot (180 OTPs) was to incorporate a number of such small OTPs. It is hoped that the pilot will yield meaningful fiscal data about the needs of such programs in meeting accreditation standards. It is certainly possible that such small operations will be able to affiliate with other currently accredited community based operations, however the development of a federal fund would assist such programs in pursuit of accreditation.

The Association recommends that the federal agencies, which have responsibilities for implementing accreditation, develop a series of technical assistance documents, which will be able to assist programs with different patient census sizes throughout the country. Such technical assistance publications would serve as “how to” documents, including model policy and procedure manuals, model diversion management plans, model quality assurance packages in addition to other elements of the

accreditation system. Such models would be provided in a clear and concise format, which could be specific to programs of different sizes. In this regard, programs would not be “reinventing the wheel” many times over throughout the United States.

Specific Recommendations in Response to the NPRM

Quality Assurance Plans

The Association supports the intent to have OTPs develop quality assurance plans to pursue continued improvement of patient care.

Diversion Control Plans

The Association also supports the proposal “that treatment programs include a Diversion Control Plan as part of the quality assurance plan.” The Association’s work with the Drug Enforcement Administration in producing a series of guidelines for improving the accountability of methadone hydrochloride products indicates our interest in ensuring that programs do all that they can to protect the health of the patients and the public.

Preventing Multiple Patient Enrollment

The Association recognizes that the proposed rule retains the existing regulation about preventing multiple enrollment. It is interesting to note that very few states have a comprehensive computer based patient registry to prevent such multiple enrollments. How does the Secretary propose to implement this system where multiple patient enrollments would be prevented?

Lifting Prohibition on LAAM Take-Home Doses

The Association understands that LAAM is provided in 279 treatment programs throughout the United States, based on the Association’s 1998 survey. LAAM has been used for a number of years in OTPs. The Association supports removing the prohibition on the unsupervised use of LAAM in programs since we believe that it would be of enormous help to the patients. Take home use of LAAM should follow the same criteria as proposed in option 2 for methadone take home doses.

Recommendations for Greater Clinical Flexibility for Methadone Take-Home Doses

The NPRM presents several options for modifying current take home medication requirements. The Association supports the intent of providing greater clinical flexibility in determining take home dosages for patients, who have met the criteria of current federal law, which are retained under the proposed rule in guiding the prescribing and dispensing of take home medication.

The Association urges the federal government to adopt a variation within option 2 following the Institute of Medicine recommendation. This variation would allow individual OTPs to dispense take home supply of medication for up to fourteen days following one year of treatment and up to a thirty-one day supply following two years of treatment, providing the patient has met the criteria as stipulated in the Proposed Rule.

SUMMARY

The Association supports the federal government's intent to shift regulatory oversight away from process oriented regulations to outcome oriented accreditation standards of care. We recommend that the federal government develop a fund to assist a treatment program in paying for such a shift in regulatory oversight in order to avoid a decrease in treatment capacity. We urge the federal government not to create a two tiered system of regulatory oversight holding OTPs accountable to accreditation standards and individual practitioners to a different and lesser standard of care. The development of such a two tiered system will create instability throughout the entire system of treatment and will be counter to the intent of the Proposed Rule.

We are hopeful that the individual states will either adopt accreditation standards or accept the results of accreditation surveys in lieu of their own state regulatory inspections as a means of avoiding duplication of effort and cost. This will require extraordinary cooperation among federal agencies and State Methadone Authorities to improve interagency communication, which has been limited in the past. Fortunately, the Center for Substance Abuse Treatment has been working with the State Methadone Authorities during the past several years to improve such interagency communication.

Our Association views the Proposed Rule as only one piece of a federal strategy to increase access to care, to improve the quality of care currently offered, to expand new opportunities for patients and to educate the public about the value of methadone treatment. It moves the system to a new place in the evolutionary chain in addiction treatment.

nrpmdraft

Appendix A

Direct/Indirect Costs of Accredited Methadone Treatment Programs

State	Florida	Michigan	Missouri	Pennsylvania	Rhode Island	Texas
Agency/ Date	JCAHO/ 1/99	JCAHO/ 9/98, 3/91, '83	JCAHO/ 4/99	JCAHO/ 9/27-29/99	JCAHO/ 10/96	JCAHO/ 1989
Application Fee	-	-	-	<i>Mock Survey</i>	-	-
Number of Surveyors	3	1	4		1	4
On-Site Cost	\$33,300.00	\$7,400.00	\$14,000.00		\$12,363.00	\$10,000.00
Accredited Services	Inpatient partial hospital, outpatient drug abuse, child/adolescent	Methadone Program and Drug Free	Outpatient methadone, adolescent alcohol/drug abuse program	Methadone, drug free outpatient, prevention, partial hospital, HIV early intervention	All drug free and maintenance	Methadone outpatient, residential, detox, mental health services
Indirect Cost	\$17,679.00 consultants and staff time	\$10,000.00 staff time/per year	\$35,000.00 staff time computer upgrade, physical plant and security upgrade	\$7,055.00	\$26,916.00 Mental Health Consultant (- infectious control manual) staff time (clinical supervisor & counselor)	\$45,000.00 hire FT staff (Community Psychologist) staff time

Note:

These data were compiled through a survey of the state provider associations, which comprise the American Methadone Treatment Association. The information on this chart represents one methadone treatment program within that state.

Appendix A (Continued)

MASSACHUSETTS

City	Fall River	New Bedford
Agency/ Date	JCAHO/ 1999	JCAHO/ 1996/1999
Application Fee	-	-
Number of Surveyors	1	4
On-Site Cost	\$3,500 - \$5,000.00 based on census of 300 patients	\$25,000.00 (multiple site fee)
Accredited Services	Methadone and Outpatient Substance Abuse	Substance Abuse and Mental Health Service, Methadone Program
Indirect Cost	\$970.00 Staff time (PI projects)	Hire QI Director - \$50k, MIS database Treatment satisfaction surveys, Staff time

NEW YORK

	Albany	Brooklyn	Long Island
Agency/ Date	JCAHO/ 11/98	JCAHO/ 3/98	JCAHO/ 1997
Application Fee	-	-	-
Number of Surveyors	4	1	1
On-site Cost	\$15,000.00	\$6,000.00	Absorbed by Hospital
Accredited Services	Article 28 Facility	Substance abuse treatment system - family health centers, ambulatory care services	Methadone Treatment
Indirect Cost	Absorbed by Hospital	Staff time, creating manuals, information systems upgrade	Staff time

Appendix A (Continued)

OHIO

City	Akron	Canton	Toledo	Youngstown
Agency/ Date	JCAHO/ 1983-1985	JCAHO/ 1970s	JCAHO/ 3/95	JCAHO/ 1993
Application Fee	-	-	-	-
Number of Surveyors	1	1	1	1
On-site Cost	\$5,600.00	\$14,000.00	\$7,500.00	\$15,600.00
Accredited Services	Entire behavioral health program - Methadone outpatient/inpatient, partial residential	Outpatient/Residential Medical/Drug Screening Methadone/Prevention	Methadone program (outpatient)	Entire program - Clinical & Medical services
Indirect Cost	Physical Plant renovations	-	\$5,000.00 Staff time	Staff time

Appendix B

State Authority Response, September 1999

State	# of Programs	# of Programs Receiving Block Grants	Excel/ Good/Fair /Poor	Violation of FDA Regs	Violation Of State Regs	Danger Of Closing	Technical Assistance (Prog./ Phys. Plant)
AL	15	2	G-13 F-2	2	0	0	PP - 5
AK	1	1	F-1	0	0	0	Prog - 1
AZ	-	Did	Not Choose	To	Complete	Inquiry	-
AR	2	1	E-1 G-1	0	0	0	PP-1 Both - 1
CA	-	Did	Not Choose	To	Complete	Inquiry	-
CO	9	5	E-4 G-5	0	0	0	Prog-3 Both - 2
CT	18	15	-	0	0	0	Both - 16
DE	2	2	G-1 F-1	0	0	0	Prog - 1
D.C.	5	2	E-2 G-2 F-1	0	0	0	Prog - 1
FL	25	5	E-5 F-20	0	0	0	Both 20
GA	19	5	E-1 G-5 F-8 P-5	0	5	1	Prog-9 PP-4 Both-4
HI	4	1	G-3 P-1	0	0	0	Both - 1
IL	43	30	E-12 G-25 F-6	0	0	0	Both 6
IN	13	2	G-13	0	0	0	Prog-13
IA	2	1	G-1 F-1	0	0	0	Prog - 2
KS	5	0	G-5	0	0	0	Prog - 5
KY	6	2	E-2 F-4	0	0	0	Prog - 6 PP - 4 Both - 4
LA	11	1	G-6 F-5	N/A	1	1	0
ME	2	0	P-2	0	1	1	Prog - 2
MD	35	18	E-10 G-11 F-6 P-8	0	2	0	Prog - 14 PP - 1 Both - 1
MA	27	11	-	0	0	0	Both - 27
MI	31	19	-	0	0	0	0
MN	6	5	E-2 G-4	0	0	0	0

APPENDIX B (Continued)

State	# of Programs	# of Programs Receiving Block Grants	Excel/Good/Fair/Poor	Violation of FDA Regs	Violation Of State Regs	Danger Of Closing	Technical Assistance (Prog./ Phys. Plant)
MO	8	4	E-1 G-3 F-3 P-1	0	1	0	Prog - 4
NE	1	1	G-1	0	0	0	0
NV	6	N/A	G-6	N/A	N/A	N/A	N/A
NJ	32	22	G-6 F-26	Unkn	Unkn	Unkn	Prog - 26
NM	11	3	E-1 G-2 F-8	0	No regs yet	0	Both - 8
NY	124	44	E-88 G-31 F-5	0	0	0	See note below
NC	13	8	E-1 G-5 F-6 P-1	1	1	0	Prog - 2
OH	9	N/A	N/A	N/A	N/A	N/A	N/A
OK	2	0	G-2	0	0	0	0
OR	13	5	E-1 G-5 F-7	0	0	0	Prog - 7
PA	28	22	E-10 G-7 F-5 P-6	1	6	0	Prog - 27
RI	8	5	E-5 F-3	0	0	0	Both - 3
SC	6	0	G-2 F-4	0	0	0	Prog - 5 PP - 3 Both - 3
TN	5	0	G-4 F-1	0	0	0	-
TX	70	12	E-17 G-30 F-17 P-6	12	23	1	Prog - 20 PP - 5 Both - 5
UT	4	2	E-2 F-2	N/A	N/A	N/A	N/A
VA	9	9	E-3 G-4 F-1 P-1	0	0	0	Prog - 1
WA	9	8	E-2 G-5 P-2	2	2	0	Prog - 3
WI	9	0	E-2 G-1 F-2 P-3	3	3	1	Prog - 3 PP - 2 Both 2
	T	O	T	A	L	S	
40/42	648	273	E - 172 G - 209 F - 145 P - 36	21	45	5	Prog-155 PP - 25 Both-103

Note: The NY programs could benefit from TA concerning the development of written comprehensive policies and procedures as well as providing treatment to patients with secondary addictions to other drugs such as cocaine.

Appendix C

Criteria for Stable Patient Referral From Methadone Programs to Office Based Medical Practice Settings “Expanding Access to Medical Maintenance Treatment”

- I** Program Involvement: We recommend the following criteria for choosing the participating agencies:
- a) Compliance with federal and state regulatory authorities.
 - b) Adherence to CSAT's State Methadone Treatment Guidelines and the American Methadone Treatment Association's Ethical Canon.
 - c) Licensed as a "Narcotic Treatment Program" for a minimum of two years.
 - d) Demonstrated internal protocols for reviewing patient eligibility, utilizing a multidisciplinary team approach including, at a minimum, the program's Medical Director, Nurse Manager, and the patient's counselor.
 - e) The program shall contract with the participating physicians.
- II** Physician Involvement: Demonstrated interest in the treatment of opioid dependent patients in his/her medical or psychiatric practices as defined by:
- a) Certification by the American Board of Psychiatry and Neurology with subspecialty certification in addiction psychiatry, certification by the American Society of Addiction Medicine or Specialty Board Certification of Physicians of the American Osteopathic Association. It is recommended that physicians with such certification sit for a course on opioid pharmacotherapy as offered by the American Methadone Treatment Association or a recognized medical society.
 - b) Physicians without such certification, but with a documented two-year involvement in a methadone treatment program, should sit for a course on opioid pharmacotherapy as offered by the American Methadone Treatment Association or a recognized medical society.
 - c) Knowledge of specific methadone prescribing practices as regulated by state and federal law.
 - d) Practices consistent with CSAT's State Methadone Treatment Guidelines.
 - e) Agreement to provide progress reports to the sponsoring "Narcotic Treatment Program".
 - f) Agreement to work with the patient and program regarding relapses or unstable patients.
 - g) Provision for urine screens.
 - h) No pending state licensure actions against the participating physician.
 - i) Proof of minimum individual professional liability coverage as required by the State Medical Board of Examiners or equivalent thereof.

III Patient Eligibility: The patient must meet the following criteria:

- a) Patient be physically and emotionally stable for 36 months.
- b) The patient should be free of alcohol and drug abuse for 36 months verified by toxicology screening.
- c) The patient has not been convicted of any criminal activity for 36 months.
- d) The patient has been employed or in a similar capacity (a student, homemaker or disabled) for 36 months as well as a stable living environment.
- e) Demonstrated responsible use of take home methadone through a participating licensed "Narcotic Treatment Program".

There may be exceptions granted to the 36 month criteria. Exceptions must be based on the individual's progress in treatment and recommendations made by the treatment team as documented in the clinical record. The process for which this decision can be made must be endorsed and reviewed by the State Regulatory Authority.

IV Organizational Issues:

1) **Professional and agency liability:**

- a) A copy of the physician's professional liability insurance would be included in the physician's file, which would be kept at the program site.
- b) Professional liability coverage would be incorporated into the contractual agreement with participating physicians.

2) **Methadone distribution to participating physicians:**

- a) The participating physicians will be registered under the umbrella of the narcotic treatment program license.
- b) A personnel file with resumes, license, registration numbers, personal professional liability insurance carrier, and contract to provide this service would be on file with the program.
- c) The administration and dispensing of methadone hydrochloride in an "off-site" physician based practice will require a change in federal and state laws and regulations.

3) **Discontinuation of off-site services:** Patients will be referred back to the base "Narcotic Treatment Program" for continued services for the following reasons:

- a) Signs and/or symptoms of recurring drug or alcohol misuse.
- b) Negative methadone urine screens or positive for drugs not appropriately prescribed.

- c) Significant changes in mental/physical/behavioral status that would require more patient supervision.
- d) Noncompliance with medical care.
- e) Evidence of criminal activity (drug or other).

(medmaexp99)

RESEARCH

Mortality associated with New South Wales methadone programs in 1994: lives lost and saved

John R M Caplehorn and Olaf H Drummer

Methadone maintenance greatly reduces heroin addicts' risk of death.¹ A 15-year follow-up of patients in New South Wales showed methadone maintenance saved lives by reducing addicts' risk of fatal heroin overdose.¹ When combined in a meta-analysis with the results of overseas cohort studies, the relative risk of death in methadone maintenance was a quarter that of addicts not in treatment (95% CI, 0.19–0.33).¹ However, methadone maintenance is also a cause of death. Patients are at risk of fatal iatrogenic toxicity and other drug users may die from taking methadone syrup diverted from maintenance programs.^{2–6}

Mortality associated with NSW maintenance programs was independently investigated. The first report from this project presented the case histories of the 13 patients who died in the first two weeks of treatment.⁷ It identified 10 probable cases of fatal iatrogenic methadone toxicity (ie, where prescribed doses of methadone either caused or contributed to fatal accidental drug toxicity).⁷ This, the second report, presents an estimate of the relative risk of fatal accidental drug toxicity in the first two weeks and later maintenance. It also presents estimates of the effect of admission to methadone maintenance on the risk of fatal accidental drug toxicity and of the number of lives saved by NSW maintenance programs in 1994.

Methods

This study was approved by the Human Research Ethics Committee of the Western Sydney Area Health Service and the NSW State Coroner.

Abstract

Objectives: To estimate the effects of methadone programs in New South Wales on mortality.

Design and cases: Retrospective, cross-sectional study of all 1994 New South Wales coronial cases in which methadone was detected in postmortem specimens taken from the deceased. Cases were people we identified as patients in NSW methadone maintenance programs or those whose deaths involved methadone syrup diverted from maintenance programs.

Outcome measures: Relative risks of fatal, accidental drug toxicity in the first two weeks of treatment and later; the number of lives lost as a result of maintenance treatment; preadmission risks and the number of lives saved by maintenance programs, calculated from data from a previous study.

Results: There was very close agreement between this study's classifications and official pathology reports of accidental drug toxicity. The relative risk (RR) of fatal accidental drug toxicity for patients in the first two weeks of methadone maintenance was 6.7 times that of heroin addicts not in treatment (95% CI RR, 3.3–13.9) and 97.8 times that of patients who had been in maintenance more than two weeks (95% CI RR, 36.7–260.5). Despite 10 people dying from iatrogenic methadone toxicity and diverted methadone syrup being involved in 26 fatalities. In 1994, NSW maintenance programs are estimated to have saved 68 lives (adjusted 95% CI, 29–128).

Conclusions: In 1994, untoward events associated with NSW methadone programs cost 36 lives in NSW. To reduce this mortality, doctors should carefully assess and closely monitor patients being admitted to methadone maintenance and limit the use of takeaway doses of methadone.

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In late 1995 the database at the NSW Health Department's Division of Analytical Laboratories was searched to identify 1994 coronial cases in which methadone was detected in postmortem specimens. These analytical laboratories receive specimens for toxicological analysis in all cases of sudden death referred to the NSW State Coroner. Autopsy, toxicology and police reports and the statements of family and friends, prescribers and other witnesses were collected from coronial files.

The methadone treatment histories of the deceased were extracted from data

held by the NSW Health Department's Pharmaceutical Services Section. The Department also provided data on the number of people admitted to and treated with methadone maintenance in NSW in 1994.

Cases were grouped according to the source of the methadone: methadone syrup given as maintenance treatment; methadone syrup diverted from the maintenance program; and methadone tablets (Physeptone; Glaxo Wellcome, Boronia, Vic.) prescribed for pain relief. As the Sydney black market consists almost entirely of methadone syrup diverted from maintenance programs,⁸ illicit drug users who obtained methadone from an unknown source were classified as having taken diverted syrup.

We used two parallel classifications of cause of death — that on the official pathologist's report, and our own. In our

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1: A case of fatal iatrogenic methadone toxicity

This 1995 NSW case highlights the danger of daily doses of 30–40 mg methadone in non-tolerant individuals and presents a classic history of fatal iatrogenic toxicity. The deceased had clear, early signs of methadone toxicity: somnolence; unsteady gait; vomiting; and a general feeling of being unwell. The terminal events were also typical: prolonged coma following sleep; very slow, deep, irregular, noisy breathing; brown pulmonary oedema fluid coming from the mouth or nose.

Six weeks before his death, the 19-year-old man was admitted to hospital with hypothermia, pneumonia, right brachial plexus neurapraxia, rhabdomyolysis and acute renal failure after a heroin overdose. He reported using amphetamines for six months and heroin for two weeks. Liver function test and echocardiogram findings were normal, and at discharge three days later his serum creatinine level had fallen from 0.18 mmol/L to 0.10 mmol/L (upper normal limit, 0.12 mmol/L).

He was referred to a short-stay, residential program and told the admitting officer he had had problems with alcohol for five years, cannabis for seven years and amphetamines for one year, but had only used heroin six times. While he was considered suitable for admission to a drug-free rehabilitation program, this was delayed pending full recovery of his arm.

However, he was advised not to wait to enter this program as he was facing trial for a criminal offence. Soon after, the deceased apparently told a general practitioner and a methadone prescriber he had been using heroin daily for a year. He was prescribed 30 mg methadone, with the dose to be increased by 5 mg every day for six days and then reviewed.

The deceased vomited several times after receiving his second

dose (35 mg). The next morning, he was difficult to rouse, had trouble walking and urinating and kept falling asleep. His father was unable to contact the methadone prescriber, who was on holiday, and the nurses at the private methadone clinic did not seem to have recognised the seriousness of the situation.

By late afternoon he felt much better and travelled by public transport to receive his last dose of methadone (35 mg) at 1830. That evening he seemed well, was in a very good mood and ate a large dinner. However, he was still having difficulty urinating. He went to bed at 2245. Around 0645 the next morning his father was unable to wake him, he was breathing deeply, noisily and irregularly and had brown fluid coming from his mouth. After about fifteen minutes he stopped breathing and died.

At autopsy, the body weighed 72 kg. No "track" or recent injection marks could be identified. The lungs weighed 960 g (right) and 860 g (left) and were described as "very oedematous and congested". The heart and liver were macroscopically and microscopically normal. The postmortem blood methadone concentration was 0.32 mg/L. No other drugs were detected in blood, bile or urine samples. The investigating pathologist determined the cause of death was methadone toxicity. The Deputy NSW State Coroner determined the fatal toxicity was caused by the administration of three daily doses of methadone (30 mg, 35 mg and 35 mg).¹³

At the inquest, the deceased's methadone prescriber said he did not physically examine methadone patients and had not rejected an applicant for maintenance in the past two years. He routinely saw methadone patients only one day a week at a private methadone clinic.¹³

classification, we initially established cause of death independently of one another, with one of us (OHD) blind to the official cause of death. Cases were first categorised as "accidental drug toxicity" and "other". The "other" category included suicides, deaths from natural causes and trauma, and deaths in which drug toxicity was considered to have contributed to a death from natural causes. The "accidental drug toxicity" cases were further categorised into "methadone" and "other drug or drugs" on the basis of whether or not methadone was considered to have either caused or made a significant contribution to the death.

There were no simple criteria for establishing the contribution of methadone to deaths involving other drugs. However, as deaths to which methadone contributed closely resembled cases of fatal methadone toxicity,^{2,3,7} a relatively confident decision could be made after a thorough exami-

nation of the documentary and toxicological evidence and the autopsy report.^{2,7,9-12}

Police statements and photographs of the deceased at the scene of death provided some assistance. A brownish, frothy oedema fluid was often observed coming from the deceased's mouth or nose (see Box 1).⁷ Witnesses' statements provided a guide to likely tolerance and chronologies of ingestion and of the development of symptoms and signs of toxicity.^{2,7} These statements were particularly useful in cases involving methadone as death usually occurred some hours after the drug was taken,¹⁴ and some time after the development of coma (see Box 1).^{2,3,7,10,11}

Postmortem blood methadone concentration was helpful but not definitive, as fatal concentration varies widely with tolerance^{11,12} and the blood concentration of methadone increases after death.¹⁵ Moreover, the postmortem increase in blood methadone concen-

tration varies unpredictably from one part of a cadaver to another.¹⁶

The autopsy findings were remarkably consistent in cases of fatal drug toxicity involving methadone, with the immediate cause of death being pulmonary oedema secondary to hypoventilation.^{2,7,10,11} As methadone toxicity usually causes a gradually worsening hypoventilation, the hypoxia and resulting pulmonary hypertension are generally prolonged and severe, and significant quantities of water and electrolytes, large proteins and red blood cells leak from the pulmonary capillaries into the air spaces. Consequently, brownish oedema fluid was often observed in the large airways and the lungs were unusually heavy (see Box 1). Microscopic examination of lung specimens often showed areas of patchy bronchopneumonia and other evidence of prolonged hypoventilation and suppression of the cough reflex.^{2,7,10}

Statistical analysis

We used published estimates of NSW methadone patients' risks of death after leaving treatment as approximations of 1994 NSW methadone patients' risks before admission to treatment.¹ Rates were adjusted for age, as the risk of death was significantly higher for those aged 20-29 years compared with those aged 30-39 years.¹ Weighted average risks were calculated in the knowledge that, in 1994, 68% of NSW maintenance patients were at least 30 years of age.¹⁷ We assumed half of those admitted to maintenance were aged 20-29 years and half 30-40 years.

The 95% confidence intervals of mortality rates were calculated by dividing the estimates by significance factors taken from a published table.¹⁸ The standard errors of the relative risks were estimated using the binomial approximation of the Poisson distribution.¹⁹

Results

Methadone was detected in postmortem material from 89 NSW coronial cases in 1994. These cases comprised 41 methadone maintenance patients (38 registered with the NSW Health Department and three with the Queensland Health Department), one neonate being breastfed by a NSW methadone maintenance patient, 29 cases considered to have involved methadone syrup diverted from the NSW methadone program, and 18 cases considered to have involved methadone tablets.

In 18 of the 29 cases involving diverted methadone syrup, either a bottle used to dispense methadone syrup (5 cases), a statement from a witness (10 cases), or both (3 cases), indicated that the maintenance program was the source of the methadone. In the remaining 11 cases, it was assumed methadone syrup was obtained from the black market.³ In 16 of the 18 cases involving methadone tablets, either a statement from the prescribing doctor (8 cases), a tablet bottle (4 cases), or both

2: Causes of death determined in this study and in official pathologists' reports for 38 patients in New South Wales methadone maintenance programs and 29 people whose deaths involved methadone diverted from maintenance programs

	Accidental drug toxicity		Other causes of death
	Methadone*	Other drug(s)	
Methadone maintenance patients			
Death in first two weeks			
This study	11	1	1
Official report	10	2	1
Death after two weeks			
This study	1	5	19
Official report	1	5	19
Diverted methadone			
This study	26	1	2
Official report	24	2	3
Totals			
This study	38	7	22
Official report	35	9	23

* Methadone either caused or contributed to the death.

(4 cases), indicated the source of the methadone. The remaining two people had professional access to methadone tablets and committed suicide.

We excluded the three Queensland maintenance patients, the neonate and all cases involving methadone tablets, leaving 67 cases in the study.

Methadone maintenance patients

Box 2 shows that, of the 38 NSW maintenance patients, 13 died in the first two weeks after admission, and 25 died later in treatment. We and the official pathol-

ogists concluded that 12 of the 13 fatalities in the first two weeks of maintenance and six of the 25 deaths later in treatment were caused by accidental toxicity. Three of six deaths from accidental drug toxicity among established maintenance patients were caused by heroin, one by dextromoramide, one by the combined effects of heroin and dextropropoxyphene, and one involved injected methadone syrup.

Diverted methadone syrup

Box 2 shows that, for the 29 cases involving diverted methadone, we concluded methadone contributed to 26 of 27 deaths from accidental drug toxicity compared with 24 of 26 on the

official pathologists' reports. One death which we classified as accidental drug toxicity was officially attributed to bronchopneumonia with methadone intoxication as a contributing factor. In another case, we concluded injected, diverted methadone contributed to a death which was officially attributed to acute heroin poisoning.

Witnesses' statements or autopsy reports indicated that methadone syrup was injected in 16 of the 26 cases we classified as accidental drug toxicity to which diverted methadone contributed. One of the 10 cases involving oral inges-

3: Rates of fatal accidental drug toxicity and relative risks of fatal accidental drug toxicity and sudden death from all causes for patients in New South Wales methadone maintenance programs in 1994

	Rate (Deaths/1000/yr)	Relative risk	95% CI
Deaths from accidental drug toxicity			
In first two weeks' maintenance	70.4		36.3-122.8
After two weeks' maintenance	0.72		0.26-1.57
First two weeks' maintenance v. out of treatment*		6.7	3.3-13.9
First two weeks' maintenance v. after two weeks' maintenance		97.8	36.7-260.5
Out of treatment* v. after two weeks' maintenance		12.2	4.8-30.6
Deaths from all causes			
Out of treatment* v. all maintenance		3.5	2.2-5.6
Out of treatment* v. after two weeks' maintenance		5.2	3.1-8.7

* Calculated from approximations derived from previously published data.

tion of diverted methadone was that of an infant who either took or was given some of his mother's syrup.

Relative risks of accidental drug toxicity

We concurred with official pathologists' conclusions that 12 patients died of accidental drug toxicity during the first two weeks of maintenance treatment in NSW in 1994 (see Box 2). To calculate the rate of fatal accidental drug toxicity, we estimated the total time patients spent in the first two weeks of maintenance treatment. In 1994, 4449 people were admitted to methadone maintenance in NSW. Assuming all new admissions stayed at least two weeks in treatment,^{20,21} patients spent approximately 170.5 person-years in the first two weeks of maintenance. Using this estimate as the denominator, the rate of fatal accidental drug toxicity in the first two weeks of maintenance was 70.4 deaths per thousand per year (Box 3).

We also agreed with official pathologists' conclusions that six NSW methadone patients died from accidental drug toxicity after being in maintenance treatment for at least two weeks (Box 2). An approximation of the total time methadone patients spent in treatment in NSW in 1994 was derived from the average of the number in treatment at the beginning and end of the year (7975 and 9038, respectively).²² The 170.5 person-years spent in the first two weeks' maintenance were subtracted from the average of the totals, 8506.5, to estimate the total time spent in later maintenance — 8336 person-years. When this was used as the denominator, the rate of fatal accidental drug toxicity in later maintenance was 0.72 deaths per thousand per year (Box 3).

When combined with the previous estimate, the risk of fatal accidental drug toxicity in the first two weeks of treatment in NSW in 1994 was estimated to have been 97.8 times the risk later in maintenance (95% CI RR, 36.7–260.5 times). Based on the results of a previous study,¹ the rate of fatal accidental drug toxicity for addicts on the street was estimated to be 10.4 per thousand per year. Using this estimate, the risk of fatal accidental drug toxicity in the first two weeks of methadone maintenance in

NSW in 1994 was 6.7 times the risk before admission (95% CI RR, 3.3–13.9 times).

Lives saved by NSW maintenance programs

The age-adjusted approximation of the expected mortality from all causes among heroin addicts was 15.5 deaths per thousand per year (95% CI, 11.0–21.9 deaths).¹ Using this estimate, 132 deaths would have been expected to occur in 8506.5 person-years (95% CI, 93–187 deaths). As 64 people either died while receiving maintenance (38) or from the toxic effects of diverted methadone (26), NSW methadone programs are estimated to have saved 68 lives in 1994 (95% CI, 29–123 lives saved). To save one life approximately 125 patients needed to be given methadone maintenance for a year (95% CI, 69–293 patients).

To adjust for possible bias, we assumed that up to three of the 11 cases classified as involving diverted methadone syrup may have actually involved methadone tablets. When added to the two cases involving diverted methadone syrup in which there were differences in the official and study classifications of cause of death (Box 2), the number of lives saved may increase by up to five. Consequently, the upper limit of the confidence interval increased to give an adjusted 95% CI of 29 to 128 lives saved.

If all 10 cases of fatal iatrogenic methadone toxicity⁷ and 26 deaths to which diverted syrup contributed had been avoided, NSW maintenance programs would have saved 104 lives in 1994 (adjusted 95% CI, 65–164 lives saved), making them up to 53% more effective at saving lives (adjusted 95% CI, 37%–124%).

Discussion

We found that, in NSW in 1994, the risk of fatal accidental drug toxicity in the first two weeks of methadone maintenance was nearly seven times the risk before admission to treatment. A previous report suggested that this excess mortality was primarily the result of iatrogenic methadone toxicity.⁷ However, the risk of fatal accidental drug

toxicity later in maintenance was approximately one-hundredth the risk in the first two weeks of treatment and less than one-tenth the risk before admission.

As there was complete agreement between our classification and that of official pathologists, our estimate of the relative risk of fatal accidental toxicity in the first two weeks and later maintenance is unlikely to have been significantly affected by misclassification of causes of death. Further, in estimating that NSW methadone programs saved 68 lives in 1994, we allowed for the difference between our opinion and that of the official report on the role of diverted methadone in two cases when calculating the upper limit of the adjusted 95% confidence interval (29–128) for the number of lives saved by NSW maintenance programs.

Another consideration in estimating the number of lives saved is that mortality among patients discharged from maintenance is only an approximation of preadmission risk. If the real risk on the streets was higher than our estimate, NSW methadone programs would have saved more lives and admission to maintenance would not have caused such a dramatic increase in the risk of fatal accidental drug toxicity. Conversely, if the real risk was lower, the reverse applies.

Our estimates of the number of lives saved and the increase in the risk of fatal accidental drug toxicity associated with admission to maintenance are approximations only. However, as our estimated 71% reduction in mortality is very similar to that observed in the US during the early 1970s, in Sweden during the 1980s, in Germany in the 1990s and Australia during the 1970s and 1980s,¹ they are probably reasonably accurate.

Previous Australian studies have also identified mortality associated with methadone programs. Eighteen people died from methadone toxicity in Western Australia in the years 1975 to 1980. However, there were virtually no such deaths after WA maintenance patients were required to take their methadone under supervision.²³ In South Australia, nine maintenance patients died from drug toxicity in the years 1984 to 1994, while 12 other people died from the toxic effects of

diverted methadone syrup.²² The number of deaths per 1000 SA maintenance patients was approximately 75% of that observed in our study. Our finding that diverted methadone syrup contributed to 26 deaths in NSW in 1994 is supported by the results of a previous investigation which suggested that diverted methadone syrup was involved in up to 100 deaths between July 1990 and December 1995.⁶

The WA experience²³ suggests the number of deaths from diverted methadone syrup is related to the number of takeaway doses dispensed to maintenance patients for consumption on subsequent days. In 1994, two-thirds of private sector patients received four takeaway doses a week, with some programs giving five or six a week to newly admitted patients.²⁴ Although the NSW Health Department argued against such practices, there was no policy enforcement.²⁴ To minimise the diversion of methadone syrup from maintenance programs, the NSW Health Department should monitor and ensure compliance with its current policy which strictly limits the number of takeaway doses available to recent admissions while giving stable, long-term patients access to generous takeaway privileges.

A serious problem with iatrogenic methadone toxicity was identified in Victoria, where 10 deaths occurred among newly admitted methadone patients in the last six months of 1989.² As Victorian methadone programs treated fewer than 1200 maintenance patients in this period, the rate of iatrogenic methadone toxicity was many times that observed in our study. It is noteworthy that, during 1989, the number of Victorian maintenance patients and programs increased rapidly and a number of inexperienced and poorly trained prescribers entered the field.²³ Persons with minimal or no tolerance were prescribed initial, daily methadone doses of 50–70 mg, with fatal results.²

Two recent British studies, from Sheffield and Manchester, have similarly identified significant numbers of deaths from iatrogenic methadone toxicity early in maintenance treatment.^{4,5} These problems also arose after the relaxation of admission criteria and during a period of rapid increase in the

numbers of maintenance patients and the involvement of new, inexperienced prescribers.^{4,5}

While the official criteria for admission to methadone maintenance in NSW have not changed since 1988,²⁵ they were not being implemented in 1994.²⁶ Statements made by its Chairman in 1996 indicate that the NSW Medical Committee had not been applying the official admission criteria for some time.²⁶ This is significant because, under the NSW Poisons Act, the Medical Committee advises the NSW Health Department on applications from doctors to prescribe methadone maintenance to addicts.

There were also problems with prescriber training. Since 1993, the NSW Methadone Prescribers' Accreditation Program has used the *Methadone prescribers' manual* as its course material.²⁷ Contrary to NSW Health Department policy,²⁵ the "Manual" states heroin users need not have a history of physiological dependence on opioids to be eligible for maintenance treatment.^{26,27} We urge the NSW Health Department to revise its *Methadone prescribers' manual*,²⁷ review prescriber training and to ensure compliance with its current admission criteria for maintenance treatment.^{25,26}

In 1994, Victorian and Queensland methadone prescribers were required to examine new patients during the first days of maintenance for signs of toxicity.^{28,29} Unfortunately, the NSW Health Department did not, and still does not, have a similar policy. Indeed, many private practitioners in NSW are only available to see maintenance patients one day a week (see Box 1), and the day-to-day supervision of patients attending public clinics is left to nurses working in busy dispensaries.

The first two weeks of methadone maintenance will always be the "danger period" owing to the difficulty in determining a safe and effective starting dose. There is wide variation in opioid-naïve individuals' response to and ability to metabolise and excrete methadone,³⁰ and applicants' self-reports of recent drug use are an unreliable measure of tolerance.⁷ Given this uncertainty and variability, it is not possible to define safe, effective starting doses of methadone.

We recommend prescribers be made aware of the risks, signs and symptoms of methadone toxicity and be required to examine newly admitted patients every day for the first one to two weeks of maintenance. People seeking methadone maintenance should be required to give written consent after being warned about the dangers of misleading their doctor and of the use of other drugs, particularly benzodiazepines.^{7,31} We believe that the forthcoming NSW *methadone maintenance treatment clinical practice guidelines* will address these issues.

We strongly recommend the establishment of independent, expert committees to investigate methadone-related deaths in States and Territories with maintenance programs. These committees should be modelled on those used to monitor anaesthesia-related deaths.

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Book Review

"Vaccinology" and molecular miracles

Vaccines, vaccination and the immune response. Gordon L Ada, Alistair J Ramsay. Philadelphia: Lippincott-Raven 1997 (xii + 247 pp., \$161). ISBN: 0-397-58761-9.

As a young intern working in Perth (Western Australia) in the late 1970s, I was struck by the different impact made by two eminent medical pioneers who simultaneously visited our remote shores. Jonas Salk — whose polio vaccine was responsible for the eradication of that disease in the United States — received little media attention, giving only the occasional radio interview, while Christian Barnard — the first surgeon to transplant a human heart — was the focus of intense media attention, with staged newspaper pictures and television coverage wherever he went. Indeed, the public health impact of vaccines, and the molecular miracles of modern vaccine biology, are still mostly taken for granted by the community.

So it is timely that two highly qualified authors, Ada and Ramsay, take us on a scholarly walk through some of these achievements and bring us up-to-date with current developments in "vaccinology". We learn that there are more than 300 vaccines in the pipeline, mostly directed towards infectious agents. The authors eloquently describe the increasing role of immunologists in vaccine design, while emphasising the importance of innate immunity in vaccine success. The need for non-specific inflammatory danger signals to elicit immunity (immunology's "dirty little secret") ensures that adju-

vants, cytokines, delivery vehicles and live vaccines are still high on the agenda of vaccine science. (The potency of an immune response depends upon the level of non-specific inflammation, which in turn helps activate lymphocytes. The dirtier the wound, the more vigorous the response; this is immunology's "dirty little secret" — a well-known phrase in immunology.) Recombinant proteins, engineered peptides and naked DNA vaccines are discussed in enough detail to enhance the book's usefulness to those interested in infectious disease and public health.

The authors write objectively about vaccine safety, an extremely important issue for all of us, highlighted by some exaggerated claims concerning side effects of the current whole-cell pertussis vaccine. Perhaps vaccine science might finally capture the public imagination as we enter a period of intense activity to develop vaccines against tumours, allergies and autoimmune diseases such as diabetes. A vaccine with efficacy against any of these conditions would have an enormous impact on healthcare expenditure. Just imagine how many more heart transplants we could carry out with the extra money saved.

At \$161 the book is a little expensive for individuals, but it is worth requesting through your local medical library.

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