

Management of 41 persons exposed to a rabid dog: unplanned experience with human diploid vaccine

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Thirty-six persons — veterinarians, technicians and students at a veterinary clinic — were unwittingly exposed to a rabid dog over a period of 2½ days. One veterinarian received a penetrating bite, two other individuals were grabbed by the dog but the skin was not penetrated, and many were exposed to saliva or urine or both. In addition, the owner of the dog and his wife and three children, while not bitten, were exposed to saliva. The diagnosis was made post mortem when specimens of the dog's brain were examined by indirect fluorescent antibody testing. All but one of the students had been vaccinated against rabies with hamster kidney vaccine, but eight members of the veterinary college's staff had not been so vaccinated. Treatment started with duck embryo vaccine; if necessary, rabies (human) immune globulin was also given. When one student reacted severely to the first dose of duck embryo vaccine permission was sought to bring a human diploid vaccine into Canada. In five patients the human diploid vaccine was substituted for the duck embryo vaccine because of severe reactions to the latter. Twenty-five staff members and the family of five received both vaccines. Reactions to the human diploid vaccine were minor and transient. Recommendations include the early licensing of the human diploid vaccine in Canada.

Trente-six personnes — vétérinaires, techniciens et étudiants d'une clinique vétérinaire — ont été inconsciemment exposés à un chien enragé au cours d'une période de 2½ jours. Un vétérinaire a reçu une morsure profonde, deux autres personnes ont été mordues par le chien sans qu'il y ait eu lésion de la peau, et plusieurs ont été exposés à la salive ou à l'urine. De plus, le propriétaire du chien et sa femme et ses trois enfants ont été exposés à la salive sans être mordus. Le diagnostic post mortem a été posé lorsque des échantillons du cerveau du chien ont été examinés par l'épreuve indirecte aux anticorps fluorescents. Tous les étudiants sauf un avaient été vaccinés contre la rage avec le vaccin produit sur rein de hamster, mais huit membres du personnel du collège vétérinaire n'avaient pas été immunisés de la sorte. Le traitement a été amorcé avec le vaccin produit sur embryon de canard; au besoin, de l'immunoglobuline (humaine) antirabique a aussi été administrée. Quand un des étudiants a eu une réaction sévère à la première dose de vaccin obtenu sur embryon de canard la permission d'importer un vaccin produit sur cellules diploïdes humaines a été demandée. Chez cinq patients le vaccin diploïde humain a été substitué au vaccin d'embryon de canard à cause des fortes réactions à ce dernier. Vingt-cinq membres du personnel et les cinq membres de la famille ont reçu les deux vaccins. Les réactions au vaccin diploïde humain ont été bénignes et transitoires. Les recommandations incluent l'autorisation immédiate de distribuer le vaccin diploïde humain au Canada.

mitted to the University Veterinary Small Animal Clinic, Saskatoon early in April 1977 with a 4-day history of vomiting. He had difficulty in walking and fell when going up or down steps. The radiologic findings suggested partial obstruction of the large bowel, but no obstruction was found at laparotomy that day. The animal was transferred to the recovery area, and the following day there was evidence of atelectasis of the left lung.

A firm diagnosis had not been made; in the differential diagnosis distemper, toxicosis, septicemia and rabies were considered. The dog's condition continued to worsen, despite treatment, and, on the second day after admission, consent for euthanasia was obtained. An autopsy was performed, and the next day a diagnosis of rabies was confirmed by fluorescent antibody testing of specimens of the dog's brain performed at the Animal Disease Research Institute, Lethbridge, Alta.

That evening the dean of the veterinary college advised the city health officer, the physician in charge of the student health centre and the head of clinical microbiology of University Hospital that a group of veterinary personnel had been exposed to a dog with rabies. He was concerned that they be advised and treated as a group, since it would be impossible for them to be managed

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A male Labrador retriever was ad-

by individual physicians. He had arranged that they attend the emergency department of University Hospital.

History of exposure and recommended treatment

We assembled the day the diagnosis of rabies was confirmed to review the situation, document the histories of exposure to the rabid dog and previous vaccination against rabies, and advise action for each individual. Present at the meeting were 30 staff members of the small animal clinic with a definite history of contact with the rabid animal but various degrees of exposure.

Since the group was composed of veterinarians, technicians and students, all of whom had a basic understanding of the situation, there was a general discussion. They were advised of the relative dangers of their exposure, the dangers inherent in receiving duck embryo vaccine (a suspension of embryonic duck tissue infected with fixed, dried, killed virus) and the requirement for their consent to receive the vaccine. After detailed exposure and vaccination histories were taken from each individual it was possible to classify them as follows (Table I):

● Group 1: seven individuals with light exposure, defined as handling of the dog without possible saliva contact, and up-to-date vaccination against rabies. This group received one dose each of duck embryo vaccine. One member of the group left for Winnipeg and received her treatment there.

● Group 2: seven individuals with heavy or uncertain exposure, defined as contact with saliva or urine of the animal, and previous but not up-to-date vaccination against rabies. Five doses of duck embryo vaccine were ordered for six individuals, and one person, who had an antibody titre of 1:40, was given a single booster injection of the vaccine.

All individuals in groups 1 and 2 had received hamster kidney vaccine (a suspension of fixed rabies virus prepared in cultures of baby hamster

kidney cells; Connaught Laboratories Ltd., Willowdale, Ont.) before exposure. The manufacturer's instructions regarding subsequent administration of a vaccine licensed for use after exposure were followed.

● Group 3: 13 individuals with heavy exposure who had either never been vaccinated against rabies or were uncertain whether they had received full primary vaccination. These individuals were advised to undergo full vaccination with duck embryo vaccine (daily subcutaneous injection of 1 ml of the vaccine for 14 days, then booster injections 10 and 21 days later). One person, a student who had been heavily exposed to the dog's saliva while inserting an endotracheal tube, was advised to receive 10 ml (20 IU/kg of body weight) of rabies (human) immune globulin (Cutter Laboratories Inc., Berkeley, California) as well; he agreed to receive 5 ml.

● Group 4: two veterinarians who had been bitten by the dog (in one the teeth had not completely penetrated the skin), did not have up-to-date vaccination against rabies and were uncertain if they had received full primary vaccination, and one veterinarian who had a cut on a finger and had been heavily exposed to the dog's urine on 2 successive days while inserting an indwelling catheter without gloving. The three were advised to undergo full vaccination with duck embryo vaccine and to receive rabies (human) immune globulin, 20 IU/kg. They refused to

receive the immune globulin, partly in the belief that the globulin would interfere with active immunization.

Six additional members of the veterinary staff did not report for treatment until 5 days after the meeting (after the intervening Easter weekend). Three, who had recently been vaccinated, had had only light exposure to the dog and were offered a single booster injection of duck embryo vaccine; one, a student, declined for medical reasons. The other three staff members were given daily injections of duck embryo vaccine until their immune status could be established.

Thus, 36 members of the veterinary clinic staff had reported exposure of various degrees to the dog. One surgeon had been bitten, and an anesthetist and a student had been grabbed by the arm, although the skin had not been completely penetrated. Seventeen others had been exposed to saliva (one to saliva and urine and another to saliva, urine and vomitus) and a further five — a surgeon, two operating room nurses, a pathologist and a toxicologist — had been exposed to urine (the toxicologist worked with both urine and tissues).

Hence, 25 of 36 staff members had been exposed through their unprotected and often scratched and abraded skin to potentially infective fluids or tissues.

Determination of immune status

Of the 36 staff members who had reported exposure to the infected dog

Table I—Details of staff exposed to a rabid dog at a veterinary clinic, and recommended treatment, Saskatoon, April 1977

Staff group*	Exposure to rabies	Pre-exposure vaccination	Recommended treatment†
1, n = 7	Light	Up to date	1 dose of DEV
2, n = 7	Heavy or uncertain	Previous but not up to date	5 doses of DEV‡
3, n = 13	Heavy	None or uncertain	Full vaccination with DEV plus, in 1 person, RIG§
4, n = 3	Particularly heavy: bite or cut	Uncertain	Full vaccination with DEV plus RIG§

*Six other staff members did not attend the first meeting of exposed staff members.

†DEV = duck embryo vaccine; RIG = rabies (human) immune globulin.

‡One individual, who had a rabies antibody titre of 1:40, received a single dose.

§Treatment with immune globulin was accepted by only one individual, in group 3, who agreed to receive 5 ml rather than the recommended 10 ml.

8 had never been vaccinated. Blood samples were taken from the other 28 before treatment was begun, and the serum was examined for rabies antibody by the indirect fluorescent antibody method¹ at the Ontario Ministry of Health virology laboratories in Toronto. Eight persons were found to have a titre of 1:10 or less.

Alternative to duck embryo vaccine

One student (no. 1, Table II), whose course of vaccination 3 years before exposure had been incomplete, consisting of two doses of hamster kidney vaccine, had a severe immediate local reaction to the first dose of duck embryo vaccine. She was unwilling to continue receiving the vaccine and was given 8 ml of rabies (human) immune globulin to carry her over until alternative procedures could be recommended and her basic rabies fluorescent antibody titre determined.

Recent publications²⁻⁵ on the merits and use of a human diploid-cell-culture vaccine, including one that described its undoubted value in a trial

in Iran,⁴ led to consideration of this vaccine as a possible alternative to duck embryo vaccine. The vaccine was known to be obtainable from the Wistar Institute, in Philadelphia, and Wellcome Research Laboratories, in Beckenham, England. It is not yet licensed in Canada. Since the reaction occurred just before the Easter weekend there was considerable difficulty in locating the appropriate persons to supply the vaccine. The director of Wellcome Research Laboratories advised the use of Mérieux vaccine, a human diploid vaccine, for the individual who could not continue receiving duck embryo vaccine, and sent six doses. Authorization for the treatment of this patient was quickly obtained from Dr. A.B. Morrison, assistant deputy minister, health protection branch, Department of National Health and Welfare, and he approved the ordering of a further 100 doses for treatment of the other exposed individuals. The shipment of six doses arrived late on Easter Sunday, and the woman received the first dose the next day. The schedule recommended is one deep subcutaneous injection of 1 ml on days 0, 3, 7

and 14, and a booster injection on days 30 and 90.

Two days after the woman received her first dose of the human diploid vaccine the group of veterinary staff was assembled to be advised that this vaccine was being made available. The latest information on the vaccine and its use in other countries was discussed, and the group was told that individuals would have to sign a special consent form prior to receiving the vaccine.

Some of the staff did not require the human diploid vaccine because their antibody protection resulting from previous vaccination was adequate. Others, however, were experiencing severe reactions that kept them at home and unable to work, and they were anxious to be vaccinated with the new vaccine, which they had heard about from a visiting British veterinarian.

Since the vaccine was made in France and licensed only in Great Britain, discussions between Canada and those two countries were required to arrange for its release and importation to Canada from France. This resulted in some delay; most of the vaccine could not be given until 2 weeks after the dog's admission to the clinic. However, the earlier shipment from Great Britain enabled us to vaccinate persons who could not continue receiving duck embryo vaccine.

Reactions to the two vaccines

Seven individuals experienced uncomfortable swelling, erythema, fatigue and influenza-like symptoms after administration of duck embryo vaccine. In five persons human diploid vaccine was substituted because of the severity of the reaction. Only one individual (no. 1, Table II) had a severe immediate local reaction to the initial dose of duck embryo vaccine. A second person (no. 2, Table II), who had received a nonpenetrating bite, refused further duck embryo vaccine after five injections and did not feel well enough to go to work. A third individual (no. 3, Table II) had a similar reaction after six inoculations. Two others (nos. 4 and 5,

Table II—Details of five individuals with a severe reaction to duck embryo vaccine

Patient no.	Pre-exposure vaccination*	Cumulative treatment received*	Date	Titre of rabies antibody†
1	HKV, 2 doses 3 years earlier	1 DEV + 8 ml RIG	7/4/77‡	1:20
		1 DEV + 8 ml RIG + 1 HDV	11/4/77	NT
		1 DEV + 8 ml RIG + 2 HDV	14/4/77	NT
		1 DEV + 8 ml RIG + 2 HDV	16/4/77	1:320
		1 DEV + 8 ml RIG + 3 HDV	30/8/77	≥1:80
2	DEV 9 years earlier	1 DEV (RIG refused)	7/4/77	<1:10
		5 DEV + 1 HDV	13/4/77	NT
		5 DEV + 1 HDV + 10 ml RIG	16/4/77	NT
		5 DEV + 1 HDV + 10 ml RIG	18/4/77	1:320
		5 DEV + 3 HDV + 10 ml RIG	22/6/77	1:160
3	HKV 2 years earlier; titre 1:40 thereafter	1 DEV	7/4/77	<1:10
		6 DEV	12/4/77	NT
		6 DEV + 1 HDV	13/4/77	NT
		6 DEV + 1 HDV	16/4/77	>1:80
		6 DEV + 2 HDV	18/4/77	NT
4	Not vaccinated	1 DEV	7/4/77	NT
		8 DEV	16/4/77	1:20
		8 DEV + 1 HDV	18/4/77	NT
		8 DEV + 2 HDV	21/4/77	NT
		8 DEV + 2 HDV	25/4/77	1:80
		8 DEV + 3 HDV	21/6/77	1:80
5	DEV 5 years earlier	1 DEV (RIG refused)	7/4/77	1:20
		8 DEV	16/4/77	>1:80
		8 DEV + 1 HDV	18/4/77	NT

*HKV = hamster kidney vaccine; HDV = human diploid-cell-culture vaccine.

†Determined by the indirect fluorescent antibody method; NT = not tested.

‡Date on which the diagnosis of rabies was confirmed and the staff first met to discuss management.

Table II) stopped receiving duck embryo vaccine after eight inoculations because of increasing reaction to the vaccine. They began receiving the human diploid vaccine 2 days later. Two individuals, despite severe reactions, continued to receive duck embryo vaccine until the supply of human diploid vaccine arrived. Nineteen others had reactions to duck embryo vaccine, experiencing mainly uncomfortable swelling without influenza-like symptoms or undue fatigue, after five to seven inoculations.

All those in whom duck embryo vaccine was replaced by the human diploid vaccine remarked on the striking difference in the way they felt and the absence of severe reactions when their treatment was changed.

Only local reactions to the human diploid vaccine were noted. The reactions, which occurred in 12 of the 29 persons inoculated, were minor (erythema, slight swelling and a small area of induration) and evanescent. One person who had reacted with fever to duck embryo vaccine experienced fever for 1 day after receiving the first dose of human diploid vaccine. Transient fever has been noted after administration of this vaccine, according to the manufacturer's explanatory leaflet.

Of the five individuals who were unable to complete a course of vaccination with duck embryo vaccine and were therefore treated with a combination of active and passive immunization two (nos. 1 and 2, Table II) had antibody titres of 1:320 9 and 11 days after treatment was begun; antibody remained detectable for months after treatment was stopped. The other three persons achieved titres of 1:80 or greater. One of the three (no. 4, Table II) was a technician who had never been vaccinated against rabies. Two months later his antibody titre was still 1:80.

In seven of the individuals who were unvaccinated at the time of exposure to the rabid dog, antibody titres were recorded following treatment with the two vaccines (Table III). Five responded after eight or nine doses of duck embryo vaccine

with titres of 1:20 to 1:40 and booster injections brought the titres to 1:80. The two others (nos. 6 and 7, Table III), both students, responded with titres of 1:10 and 1:20 after 8 and 10 doses, respectively, of duck embryo vaccine; booster injections of human diploid vaccine did not help to raise their titres above 1:40, and the levels had dropped 3 to 4 months later.

Details of dog's owners

The owners of the rabid dog were treaty Indians living on a reserve 32 km south of Saskatoon, in the Dundurn area. The history of the dog's illness and family contact was obtained from the mother of the family.

The dog had started to salivate profusely 3 days before admission. At that time he was inactive and did not want to play with the children in the family. One of them, seeing

that the dog was having difficulty in eating, attempted to help him by holding the dish up to him or pushing the dog's head down to the dish. The father was exposed to the dog's saliva when he attempted to feed the dog by hand. The dog did not bite any member of the family.

The regional medical health officer notified the owners that their dog had had rabies and sent a nurse to see them 1 day after the diagnosis was confirmed. The father, when told of the diagnosis, did not at first believe that the dog had been rabid and was unwilling to have his family vaccinated. He and his wife were persuaded to be vaccinated and received their first dose of duck embryo vaccine 2 days later. A further 2 days later all the members of the family presented themselves to be vaccinated. In view of the delay in their acceptance of vaccination it was hoped that they could be given human diploid vaccine as soon as possible. It was decided 3 days later to give the parents two of the doses of the new vaccine received from Great Britain to increase their antigenic stimulus, since they had had the greatest exposure, as well as 5 ml of rabies (human) immune globulin. When the shipment arrived from France 3 days later the children also began receiving the vaccine.

The mother and the three children showed antibody titres of 1:40; the father's titre was 1:80 even though he missed two of the daily doses of duck embryo vaccine. These titres were achieved almost 4 weeks after the date of exposure. All members of the family received four doses of human diploid vaccine but could not be persuaded to accept more.

Possible source of infection

The family also owned a female Border collie. Both the dogs had roamed widely, and when the collie was in heat they roamed over a 3-km area and were seen with a large German shepherd that had been "found dead with foam on its mouth" a month before their dog became ill. This dog had been buried. The federal veterinarian investigated this

Table III—Details of seven individuals* who were unvaccinated at the time of exposure to the rabid dog

Patient no.	Cumulative treatment received	Date	Titre of rabies antibody
1	Nil	7/4/77	NT
	9 DEV	16/4/77	1:40
	11 DEV + 1 HDV	25/4/77	1:80
	11 DEV + 2 HDV	21/6/77	1:80
2	Nil	7/4/77	NT
	9 DEV	16/4/77	1:40
	12 DEV + 1 HDV	22/4/77	≥1:80
	12 DEV + 2 HDV	26/4/77	1:160
3	Nil	7/4/77	NT
	8 DEV	16/4/77	1:20
	8 DEV + 1 HDV	25/4/77	1:80
	8 DEV + 3 HDV	21/6/77	1:80
4	Nil	8/4/77	NT
	8 DEV	16/4/77	1:20
	11 DEV + 1 HDV	22/4/77	1:80
5	Nil	7/4/77	NT
	8 DEV	16/4/77	1:20
	11 DEV + 2 HDV	26/4/77	1:80
	11 DEV + 3 HDV	22/6/77	1:40
6	Nil	8/4/77	NT
	8 DEV	16/4/77	1:10
	10 DEV + 2 HDV	25/4/77	1:40
	10 DEV + 3 HDV	7/7/77	1:10
7	Nil	7/4/77	NT
	10 DEV	17/4/77	1:20
	11 DEV + 2 HDV	26/4/77	1:40
	11 DEV + 4 HDV	21/8/77	1:20

*One other individual, a veterinarian, left the group and completed full vaccination with duck embryo vaccine in the United States.

story, since the German shepherd could have been the original source of infection. The dog was exhumed and the brain examined, but it proved to be negative for rabies by immunofluorescence testing.

It seemed most likely that the source of infection was a skunk, for there was a 30% incidence of rabies in skunks in that area; furthermore, a skunk that had been killed by another dog nearby had been shown to have rabies.

The Indian reserve is close to a military camp, and since the personnel have pets it seemed wise to alert the medical officer of the camp that rabies had been diagnosed in a dog in the adjacent area. The veterinary clinic in Saskatoon arranged a vaccination clinic in Dundurn and vaccinated 125 dogs and cats. The provincial epidemiologist and the director of the regional health services branch of the Department of Health, Saskatchewan were informed of the situation and a vaccination program for dogs on the reserve was discussed.

Discussion

Incidents of this nature, while not common, have occurred when a rabid dog or horse has been handled by a large group in a teaching institution (W.G. Winkler, Center for Disease Control, Atlanta, Georgia: personal communication, 1977). All but one of the students at the Saskatoon clinic who handled the rabid dog had recently received hamster kidney vaccination and booster inoculations. However, among the veterinary college staff two veterinarians and five technicians had not been vaccinated. The veterinarians, one of whom was doing research and one postgraduate student, had handled the dog. Two of the technicians had been exposed while working in the operating room, and one other, a toxicologist, had worked with tissues from the rabid animal.

Thus, 8 of 36 staff members (22%) had never been vaccinated against rabies and were exposed to the dog or its tissues. Another eight staff members were considered non-immune at the time of exposure, for

their antibody titres were 1:10 or less; included were three veterinarians, one of whom had received no vaccine or booster injections for 9 years, and two of whom had received none for 4 years. In total, 44% of the veterinary personnel who presented themselves for treatment had been unprotected against rabies at the time of exposure, and it was mainly the veterinary college staff members rather than the students that lacked protection.

Five doses of duck embryo vaccine were ordered for eight individuals who had recently been vaccinated but had been heavily exposed to the dog's saliva; in each individual antibody titres greater than 1:80 developed after five or six doses. Two others who had recently been vaccinated but had had light exposure were found to have titres of 1:2560 and 1:640 after a single dose of duck embryo vaccine.

The person at greatest risk of acquiring rabies was the veterinary surgeon who had received a penetrating bite of the left hand 3 days before requesting treatment. He had been vaccinated 8 years previously, and his antibody titre was 1:20. Following the administration of nine doses of duck embryo vaccine the titre rose to 1:80, and 22 days after the bite, following the administration of a total of 11 doses of duck embryo vaccine and 2 doses of human diploid vaccine, the titre was 1:160. The surgeon received one more dose of human diploid vaccine, and 2 months later his titre was still 1:160.

The stimulus to obtain the human diploid vaccine was an allergic reaction to duck embryo vaccine in a student who 3 years prior to exposure had been vaccinated inadequately, receiving two doses of hamster kidney vaccine and no booster injections, yet had an antibody titre at the time of exposure of 1:20. This indicates that hamster kidney vaccine has excellent potency, and that this individual's ability to mount an antibody response was considerable.

Our experience with the human diploid vaccine confirms the reports of others²⁻⁴ that the reactions to this vaccine are minimal; we believe that

its use in Canada on a limited basis in special centres, with assurance of full documentation, is warranted. There is often a problem in getting individuals exposed to rabies to return for a series of injections of duck embryo vaccine,⁵ and with the currently recommended schedule of one injection daily for 23 days, an increase from the past, this problem is likely to worsen. Compliance with the schedule for human diploid vaccine, a total of six injections, would undoubtedly be better. This vaccine would also be of particular value when there had been a delay in reporting exposure to rabies.

To facilitate the management of similar episodes, we recommend the following:

- Vaccination against rabies should be offered to all veterinary staff members.

- Complete rabies vaccination records, including antibody titres, should be readily available.

- Booster injections of vaccine should be given on schedule and titres should be recorded.

- Hand-washing facilities and examination techniques in veterinary clinics should be reviewed, and greater use of disposable gloves should be made when exposure to rabies is possible.

- The early licensing of rabies human diploid vaccine for use in special centres should be considered if the vaccine cannot yet be made freely available.

We are indebted to Dr. W.A. Baker and his emergency department staff for their help in treating the individuals; Dr. E.M. Richards, who supplied information on the immunization status of the students; Dr. G.W. Piper, medical health officer, Saskatoon Rural Health Region; Dr. D.S. Harold, federal veterinarian, who provided follow-up information on the rabid dog and the possible source of infection; and Dr. S.J. Withrow, department of veterinary clinical studies, who provided information about the staff's degree of exposure to possible infection.

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Addendum

Since this paper was written it has come to our attention that a limited supply of human diploid vaccine is available in Canada for emergency use, subject in each instance to the approval of the bureau of drugs, Department of National Health and Welfare. The National Advisory Committee on Immunization has recommended that this supply be used for persons with serious hypersensitivity to duck embryo vaccine or Semple vaccine. Requests for the vaccine should be directed to the appropriate provincial epidemiologist or territorial or federal health department authority (*Can Dis Wkly Rep* 5: 37, 1979).

BOOKS

continued from page 1043

ATLAS OF THE ULTRASTRUCTURE OF HUMAN BREAST DISEASES. Ali Ahmed. 182 pp. Illust. Churchill Livingstone, Edinburgh; Longman Canada Limited, Don Mills, Ont., 1978. \$52.25. ISBN 0-443-01591-0

BROWNE'S ANTENATAL CARE. 11th ed. J.C. McClure Browne and Geoffrey Dixon. 448 pp. Illust. Churchill Livingstone, Edinburgh; Longman Canada Limited, Don Mills, Ont., 1978. \$30. ISBN 0-443-01476-0

CIRCULATORY DISEASES OF THE LIMBS: A PRIMER. David I. Abramson. 367 pp. Illust. Grune & Stratton, Inc., New York; Longman Canada Limited, Don Mills, Ont., 1978. \$23.75. ISBN 0-8089-1064-7

THE CLINICAL APPRENTICE. A Handbook of Bedside Methods. 5th ed. John M. Naish, Alan E. Read and Christopher J. Burns-Cox. 288 pp. Illust. J. Wright & Sons Ltd., Bristol, 1978. Price not stated, paperbound. ISBN 0-7236-0500-9

continued on page 1094

◇ Talwin* Tablets

pentazocine hydrochloride tablets N.F.

INDICATIONS: Talwin (pentazocine hydrochloride) is indicated for the relief of chronic or acute pain of moderate to severe degree.

CONTRAINDICATIONS: Talwin (pentazocine hydrochloride) should not be administered to patients with known hypersensitivity to pentazocine.

Use in Pregnancy: The use of Talwin in women of childbearing potential requires that the expected benefit of the drug be weighed against the potential risk to the mother and fetus.

Use in Children: Clinical experience in children under 12 years of age is limited, therefore, use of Talwin is not recommended in this age group.

WARNINGS:

Drug Dependence: There have been reported instances of psychological and physical dependence upon parenteral Talwin (pentazocine lactate). These reports have primarily concerned patients with a previous history of drug abuse, although there have been instances reported in patients without such a history. Usually there was a description of an increase in the dose and frequency of administration by the patient. In these patients abrupt discontinuance of the drug often resulted in withdrawal symptoms including abdominal cramps, elevated temperatures, rhinorrhoea, restlessness, anxiety and lacrimation. There have been reports of dependence upon oral Talwin (pentazocine hydrochloride). Consequently, patients who may be prone to excessive usage of drugs should be supervised carefully during oral Talwin therapy. During chronic use of Talwin, the physician should avoid unnecessary escalation of the dose and should take precautions to avoid increases in dose by the patient. Physicians should warn the patient against the use of Talwin in the anticipation of pain.

Head Injury & Increased Intracranial Pressure: The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Talwin can produce effects which may obscure the clinical course of patients with head injuries. Talwin must be used with caution in such patients, and only if its use is deemed essential.

Acute CNS Manifestations: There have been reported instances of the acute onset of hallucinations (usually visual), disorientation, and confusion in patients receiving therapeutic doses of Talwin. These manifestations have cleared spontaneously within hours upon discontinuation of the drug. The mechanism responsible for this reaction is not known. Patients demonstrating this reaction should be closely observed and if therapy with Talwin is to be restarted, administration should proceed cautiously since the acute CNS manifestations may recur.

PRECAUTIONS:

Ambulatory Patients: Since CNS effects have been noted with the use of Talwin (pentazocine hydrochloride) ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Patients Dependent on Narcotics: Because Talwin is a weak narcotic antagonist, patients who are addicted to narcotics may experience withdrawal symptoms and therefore, Talwin should be given with special caution to such persons. In non-addicted patients receiving narcotics for a short period, symptoms believed to be related to antagonism may be observed. Intolerance or untoward reactions are usually not observed following administration of Talwin to patients who have received single doses of or who have had limited exposure to narcotics.

Impaired Renal or Hepatic Function: Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Ex-

tensive liver disease appears to predispose to a higher incidence of side effects (e.g. marked apprehension, anxiety, dizziness, sleepiness) with the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Sphincter of Oddi: Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients with acute cholecystitis or pancreatitis or in those about to undergo surgery of the biliary tract.

Obstructive Uropathy: Because urinary retention has been observed in a few patients receiving Talwin, caution is advised in administration of the drug to patients with obstructive uropathy.

Respiratory Conditions: Respiratory depression has rarely been reported after oral administration, however, Talwin should be administered cautiously to patients with respiratory depression due to any cause, severely limited respiratory reserve, severe bronchial asthma, other obstructive respiratory conditions or cyanosis.

ADVERSE REACTIONS: The most frequently observed reactions after oral administration of Talwin (pentazocine hydrochloride) are sedation or somnolence, vertigo, nausea and vomiting, each of which may occur in approximately 15% of patients. Sedation may be more marked in the elderly. Less frequent reactions have been: — **Gastrointestinal** — constipation, abdominal distress, anorexia and diarrhoea; **CNS** — euphoria, lightheadedness, headache, dizziness, weakness, disturbed dreams, hallucinations (see Acute CNS effects in Warnings), visual disturbances, insomnia, tinnitus, irritability, excitement; **Autonomic** — sweating, infrequently flushing or chills; **Cardiovascular** — infrequently fall in blood pressure, tachycardia; **Allergic** — infrequently rash and rarely urticaria, erythema and oedema; **Haematologic** — rarely depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. **Other** — pruritus, alterations in maturation. Scattered reports of abnormal liver function of questionable significance were noted during the clinical trials. Hallucinations were noted to occur more frequently when doses exceeding that recommended were employed.

DOSAGE AND ADMINISTRATION:

Talwin Tablets: The usual adult starting dose is 50 mg every 4 hours after meals. Dosage should be adjusted to individual requirements and tolerance within the range of 50-100 mg (1-2 tabs) every 3 to 4 hours.

Concomitant Medication: When anti-inflammatory or antipyretic effects are desired in addition to analgesia, A.S.A. can be administered concomitantly with Talwin.

In light of the tendency to marked sedation among the elderly dosage should be kept low in this group of patients.

Duration of Therapy: There have been rare reports of withdrawal symptoms upon abrupt discontinuance of Talwin therapy after prolonged administration of the product for chronic pain. Therefore, it would be prudent to reduce the dose gradually when the drug is no longer required.

DOSAGE FORM:

Talwin Oral: Scored peach tablets of 50 mg, bottles of 100 and 500; also available as individually stripped tablets, packages of 24. Each tablet contains Talwin (pentazocine hydrochloride) equivalent to 50mg base.

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