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THE NOVA SCOTIA MEDICAL BULLETIN

The Call of Terry Fox

"Nil Desperandum"

— Horace VII 27

Rarely has the public been more stirred into sympathetic activity than by the story of this young man. Faced with the awesome problems of adjusting to an above knee amputation for a malignant bone tumor of his leg and all the attendant complications, Terry set out on an across Canada hike gathering momentum and pledges like the proverbial snowball. Running with a present day prosthesis is not easy and accomplishing 25 miles a day represents Olympian determination. As he rests after undergoing extensive chemotherapy treatment in British Columbia, he can be satisfied that he has stimulated a fantastic outpouring of sympathy for all cancer sufferers and an urgent need to improve their lot, as well as a keen interest in the disabled.

Terry has precipitated a change in attitude of the Government and the public towards cancer treatment and has brought new hope that cancer can be defeated. Millions of dollars already pledged to the Canadian Cancer Society will surely stimulate research and bring improved methods of treatment and prevention of cancer. Much needs to be done to coordinate all investigations and apply even the present known methods to our patients.

PRESENT PROBLEMS OF BONE TUMORS

Tumors such as osteogenic sarcomas which arise in bone and produce malignant bone have traditionally an extremly poor prognosis. Bone registers such as those at the Mayo Clinic showed that incidence is approximately one per hundred thousand population and the prognosis (before the advent of Chemotherapy) was approximately 20% five year 'cure' after amputation. Even this was regarded by many people as too optimistic.

The story was all to familiar to the orthopaedic surgeons — a young man would present with a bony swelling of his femur or tibia. Roentgenograms would reveal a bony irregular mass complete with Codman's reactive triangle and sun ray spicules, and would be demonstrated as an interesting case. Amputation would be carried out after biopsy had confirmed the diagnosis. Conventional radiotherapy, hyperbaric oxygen, ultra high dose radiotherapy (as advocated by Sir Stanford Cade) failed to change the prognosis appreciably. Those patients who did survive were often found to have a different type of tumor such as chondrosarcoma, fibrosarcoma or parasteal sarcoma (a particular type of osteosarcoma of peripheral excentric bone origin).

During the past decade a new hope arose. An occasional patient did survive for more than two years and if so he was more likely to continue living without recurrence. Even spontaneous regression of metastases was reported and surgical removal of pulmonary metastases was occasionally successful.

Attempts to stimulate immunity against the bone tumor were first attempted by Coley.[1] Curiously enough it was noted that patients with erysipelas might recover from cancer. In fact, in 1864 (even before the Streptococcus was discovered) a patient with cancer was placed in a bed well known to be associated with the erysipelas contagion in an effort to stimulate the appropriate anti-cancer response! Coley's toxins were subsequently extracted from *Bacillus prodigiosus* and were used to treat bone tumors, but with disappointing results. A recent application of immunotherapy has been the use of lympocytes sensitized against the patient's tumor.[2] The results of immunotherapy have been less promising than chemotherapy which has become more complex and demanding to the physician and patient than almost any other form of treatment.

The current mode is to first define the state and extent of the tumor and its spread, by appropriate clinical radiological examination and bone scans, augmented by direct biopsy of the tumor and the histological appraisal. Primary amputation or wide extensive tumor resection is followed by chemotherapy and radiotherapy.

Adriamycin (derived from the streptomyces organisms) is given in repeated doses of three days for six months.[3] The total dose is limited because of the myopathic effect on the heart. More demanding than Adriamycin, the course of Methotextrate must be given for a year.[4] The treatment dose far exceeds the lethal dose and is often given with Vincristine to augment its effect. Rescue of the patient is carried out by the use of the citrovorum factor two hours after the administration of Methotextrate. The patient is thus suspended between poison and antidote in a bizzare form of personal chemical warfare. Complications of Methotextrate administration are a loss of hair, nausea, vomiting and a possible increased susceptibility to leukemia and other blood diseases. Various differing drug regimens have been described.[5 6]

IMPACT ON THE PATIENT

It does not require much imagination to appreciate impact of the revelation of the nature of an osteosarcoma and the implications of the treatment it must have, on individual patients. Besides facing up to a doubtful prognosis, he or she must face an amputation or an extreme surgical procedure. Then there is the period of rehabilitation with a prosthesis and the continual trial of returning for unpleasant therapy each month for at least a year.

UNSUNG HEROES

There are many Terry Foxes who do not make the headlines. In Nova Scotia during the past two years many patients have accepted the different drastic regimens for the treatment of cancer. They have faced all the barriers cheerfully, acknowledging the chances of cure are dramatically better than the dismal record prior to chemotherapy. In bone cancer for example, a physician has returned to his practice, teaches in the University, and regularly walks three miles a day with his prosthesis. A young pastor faced with a potentially malignant angiomatous bone tumor submitted to above knee amputation and a prolonged course of chemotherapy. He was able to return to his parish and conduct his usual Sunday service, arranging to time his chemotherapy so that he had recovered from its toxic effects before his sermon was due.

There are hundreds of other cancer sufferers and disabled people who bravely overcome severe handicaps. Paraplegics and quadriplegics are carrying on active jobs and hold responsible positions. One of the most remarkable examples is a young man who suffers from fragilitas ossium and has experienced some two hundred fractures. He is now 24 years old and spent most of his childhood in hospital. He is barely four feet tall and he has adjusted to his tiny body so well that he drove in a specially modified van across Canada and works regularly as a laboratory technician.

CANCER TREATMENT IN NOVA SCOTIA

There are about 2,500 new cases of cancer occurring in Nova Scotia each year. The Cancer Clinic in Halifax treats about half of these patients and was founded in 1950. The Cancer Registry organized by Dr. J. A. Myrdon registers all cases of cancer. In this issue, two articles on gynecological cancer illustrate the advances achieved in this field — Dr. A. E. Bent's and Dr. M. G. Tomkin's report on the management of ovarian cancer and the article by Dr. R. C. Fraser on the work of the trophoblastic disease register.

CANCER TREATMENT & RESEARCH FOUNDATION

This newly formed organization will be based in Halifax and will be available to all patients. The foundation will coordinate cancer management throughout the Province and will act as a Referral Clinic. It will organize teaching and training of physicians in the latest methods and make the latest surgery, radiation and chemotherapy regimens available throughout the Province. A new Radiation Oncology section is being formed and is awaiting the appointment of a new dynamic leader.

TOTAL IMPACT

The heroic efforts of Terry Fox should have a tremendous effect upon the attitudes and efforts to treat cancer and assist the disabled. Much remains to be done. Spinal injuries require a special centre and research into their basic management stimulated. Multiple Sclerosis remains an unsolved problem. Prosthetics need improving and should be financed by Government so that the amputee does not have this financial burden. Above all, it is the organization, research and management of cancer that this brave young man has jerked out of lethargy into a vigorous action. □

B.J.S.G

References

1. **Coley, B L:** *Neoplasms of bone and related conditions.* 2nd Edition. New York, Hoeber, 1960, pg. 648.
2. **Neff, J R and Ennering, W F:** Adoptive immunotherapy in primary osteosarcoma. *J Bone and Joint Surg.* **57-A:** 145-148, 1975.
3. **Corter, E P** *et al.:* Amputation and Adriamycin in primary osteosarcoma. *New Eng. Med. J.* **291:** 998-1001, 1974.
4. **Jaffe, N** *et al.:* Adjuvant Methotextrate and citrovorum-factor in osteogenic sarcoma. *New Eng. J. Med.* **291:** 994-997, 1974.
5. **Sutow, W W** *et al.:* Multidrug chemotherapy in primary treatment of osteosarcoma. *J Bone and Joint Surg.* **58-A:** 629-635, 1976.
6. Editorial: Advances in the treatment of osteosarcoma. *J Bone and Joint Surg.* **58-A:** 267, 1976.

Cancer of the Ovary

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SUMMARY

Ovarian malignancy is the most common fatal gynecological cancer. We believe that an important concept in controlling this disease is yearly pelvic examination done at the time of the annual Pap smear. Improved survival and quality of life will result from early diagnosis, a better understanding of the disease process, and newer chemotherapeutic agents and treatment protocols.

INTRODUCTION

Cancer of the ovary is the most common fatal gynecologic cancer.[1] One percent of women are destined to die from this disease, and of the 1.4% of women who contract cancer of the ovary, 15 - 30% survive five years.[2]

In spite of continuing advances in the field of chemotherapy, early diagnosis is the major way in which survival can be improved and the practising physician is the cornerstone. In our opinion the annual Pap smear is of value in the detection of cellular atypia but, perhaps of equal value, is the complete bimanual rectovaginal examination which accompanies the Pap smear. Fifty percent of women at risk in Nova Scotia fail to present themselves for these examinations. At the time of examination the physician can obtain a full functional enquiry, and screen for other problems including hypertension, cancer of the breast, and cancer of the rectum. Women who have already had a hysterectomy may be reluctant to appear for yearly examinations, and yet twenty percent of cancers of the ovary occur in women who have previously had hysterectomy. The appearance of an adnexal mass in a postmenopausal woman requires immediate attention to rule out cancer of the ovary.

OCCURRENCE

Seven percent of women develop ovarian tumors of which 15-20% are malignant. Four percent of all tumors occur in children, and 50% of these are malignant. In the age group under 45 years, 6% of tumors are malignant; however, between the ages of 45 and 74 years, 33% of ovarian tumors are malignant, and 70% of these are already far advanced.[3] Cancer of the ovary most frequently occurs in women 55-65 years of age.

SYMPTOMS

The most common presenting complaint is abdominal enlargement which the patient interprets as tightening of her clothes. Nonspecific pressure and pain may also occur in up to 50% of women. Other symptoms include menstrual irregularity or uterine bleeding, bowel and bladder symptoms, leg edema, weight loss, inguinal node enlargement, and no symptoms at all in up to 10% of cases.[1,4]

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DIAGNOSIS

Because there are no known markers or laboratory tests to screen or identify women at risk for ovarian malignancy, early diagnosis may be facilitated by regular pelvic examinations in asymptomatic women, with more complete evaluation in those with any of the nonspecific symptoms. An identified pelvic mass needs full assessment, which may include an early laparotomy. Laboratory aids can be helpful in the diagnosis. Ultrasound is employed in symptomatic or obese women when pelvic masses are not readily palpable.[5] There is no place for delay in the presence of a palpable abnormality, realizing at the same time that the differential diagnosis of a pelvic mass includes many possibilities.[3,4] (Table I)

TABLE I

DIFFERENTIAL DIAGNOSIS OF A PELVIC MASS

A.	**Adnexa**	1. paraovarian cyst 2. tuboovarian abscess 3. hydrosalpinx
B.	**Uterus**	1. pedunculated myoma 2. intraligamentous myoma 3. hematometra or pyometra
C.	**Pregnancy**	1. ectopic 2. bicornuate uterus 3. normal pregnant uterus 4. molar pregnancy 5. hydramnios
D.	**Bowel**	1. carcinoma sigmoid (colon): lymphoma 2. diverticulitis 3. appendiceal abscess 4. adherent small bowel 5. hard feces in bowel 6. low lying caecum 7. redundant sigmoid colon
E.	**Urinary Tract**	1. full bladder 2. pelvic kidney 3. polycystic kidney 4. urachal cyst
F.	**General**	1 retroperitoneal mass 2. ascites 3. cyst or tumor of abdominal wall
G.	**Pelvic Abscess**	1. post-partum 2. post-abortal 3. post-operative (R/O sponge)
H.	**Ovarian**	1. nonneoplastic cyst 2. neoplastic

STAGING

Ovarian carcinoma spreads by local extension, lymphatic invasion and metastases, intraperitoneal extension or implantation, hematogenous dissemination, and transdiaphragmatic passage.[6]

As with all malignant disease, optimal treatment and analysis of results depends on accurate staging. (Table II) At the time of initial laparotomy, the proper sequence includes peritoneal washings, clinical assessment of ascites and intra-abdominal structures including liver, diaphragms, bowel, mensentery, kidneys, paracolic gutters, pelvic and paraaortic lymph glands, and biopsy of suspicious areas. Surgical treatment consists of hysterectomy, bilateral salpingo-oophorectomy and omentectomy, with biopsies of pelvic peritoneum including paracolic gutters. The importance of the initial staging is reflected in the findings of the Ovarian Study Group, which has analyzed the percentage incidence and sites of metastases demonstrated by additional diagnostic studies in patients with ovarian cancer thought to be free of disease after a limited initial exploration.[7] (Table III)

TABLE II

FIGO CLASSIFICATION OF CARCINOMA OF THE OVARY

Stage I	Growth limited to ovaries.
IA	One ovary, no ascites, 1. no tumor on external surface, capsule intact, 2. tumor present on external surface, or capsule ruptured, or both.
IB	Both ovaries, no ascites, 1. no tumor on external surface, capsule intact, 2. tumor present on external surface, or capsule ruptured, or both.
IC	One or both ovaries with ascites or positive peritoneal washings.
Stage II	Growth includes pelvic extension.
IIA	Extension or metastases to uterus and/or tubes.
IIB	Extension to other pelvic tissues.
IIC	IIA or IIB with ascites or positive washings.
Stage III	Growth may include intraperitoneal metastases outside pelvis, positive retroperitoneal nodes, extension to small bowel or omentum.
Stage IV	Distant metastases as in parenchymal liver involvement or pleural effusion with malignant cells.
Special Category	Unexplored cases that are thought to be ovarian carcinoma.

TABLE III

ADDITIONAL SITES METASTASES FOUND AFTER LIMITED INITIAL EXPLORATION

Site	Percent
Pelvic peritoneum	21
Peritoneal washings	20
Other pelvic tissue	17
Para aortic nodes	14
Diaphragm	8
Other abdominal tissue	8

HISTOLOGY

The origin of neoplastic ovarian cysts[1] (Table IV) and detailed histology (Table V) are determined following biopsy. Since the majority of ovarian tumors are epithelial, discussion of management will be restricted to this group.

TABLE IV

NEOPLASTIC OVARIAN CYSTS

Origin	Incidence %
Germinal epithelial	75
Germ cell	15
Gonadal Stromal	5
Miscellaneous	5

TABLE V

HISTOLOGY — MALIGNANT TUMORS

A.	PRIMARY	
	1. **Epithelial Tumors**	
	(a) Serous cystadenocarcinoma	50%
	(b) Pseudomucinous cystadenocarcinoma	10%
	(c) Adenocarcinoma and undifferentiated	30%
	2. **Germ Cell Tumors**	
	(a) Choriocarcinoma	rare
	(b) Malignant teratoma	2%
	(c) Dysgerminoma	1%
	(d) Endodermal sinus tumor	rare
	(e) Gynandroblastoma	rare
	3. **Special Morphology and Function or Sex Chord Mesenchyme**	
	(a) ***Feminizing Types*** (most benign)	
	i. granulosa	3-4%
	ii. granulosa-theca	1%
	iii. non-specific	1%
	(b) ***Virilizing Types*** (most benign)	
	i. sertoli-leydig; arrhenoblastoma	1%
	ii. lipid cell	1%
	iii. non-specific	1%
	iv. gonadoblastoma	1%
	4. **Connective Tissue Tumors**	
	(a) Mesonephroma	rare
	(b) Sarcoma	rare
	(c) Lymphosarcoma	rare
	(d) Fibrosarcoma	rare
	(e) Other	rare
B.	SECONDARY	
	1. Krukenberg (GI tract)	
	2. Choriocarcinoma	
	3. Other (mestastatic) (breast to ovary)	9-10%

MANAGEMENT

Ovarian enlargement occurs frequently and therefore many patients are treated in peripheral hospitals by general surgeons. All treatment options must be discussed prior to surgery because the extent of disease may only be defined at laparotomy. Identification of bowel dysfunction with diagnostic survey and preoperative bowel preparation are essential. At the time of surgery an incision which allows for easy access to the total abdomen, is required for proper assessment and maximum surgery. When doubtful etiology of the ovarian enlargement exists, a consultation with a pathologist, and frozen sections will help to identify accurately the nature and stage of disease.

If doubt persists it is prudent to do the least possible surgery in young women, confirm by permanent sections and, if necessary, reoperate at a later date. However, in

women over the age of 45, a total hysterectomy and bilateral oophorectomy is recommended. In a young patient desirous of childbearing with a Stage 1A, Grade 1 tumor, confirmed if necessary by frozen section, there is a place for unilateral salpingo-oophorectomy. Otherwise, the ideal surgical management consists of peritoneal washings, abdominal hysterectomy, bilateral salpingo-oophorectomy, and biopsies of omentum, paracolic gutters and nodes. If all the tumor cannot be removed, the objective is maximum tumor reduction to decrease the bulk of the tumor to less than 2 cm in any one area. Some cases may be deemed inoperable in which instance biopsies are taken and clinical evaluation made of the extent of the disease.

During the post-operative period, with histological confirmation of malignancy and tumor type, treatment options should be planned. Primary post-operative treatment of ovarian disease is chemotherapy, while radiotherapy now plays a lesser role. Except in some rare cases of Stage I and Stage II disease, further evaluation and treatment requires specialized expertise, which is offered by the Nova Scotia Tumor Clinic — Gynecology Disposition Clinic.

Primary post-operative treatment is continually changing with newer drugs and regimens being instituted. At one time, Melphelan (an alkylating drug in oral form) was prescribed for all advanced epithelial tumors in a dose of 8 mg/m^2/day, in three divided doses for 4 days, every 4 weeks. This agent was well tolerated, with major side effects consisting of bone marrow suppression and partial alopecia. An initial response rate of 50 to 60 percent was obtained. Currently, the first line chemotherapeutic agent is a combination of intravenous Cisplatinum and Adriamycin 50 mg/m^2 each, every 4 weeks, and the response rates appear to be better initially (70-80% in some centers).[8] For women who have not responded to previous chemotherapy, a 30 to 35 percent response rate has been achieved with this regime. The improved results are at the expense of severe side effects in the form of bone marrow suppression, intense nausea and vomiting during treatment, complete alopecia, hepatic toxicity, renal toxicity, cardiac toxicity, and auditory impairment. Other chemotherapeutic agents used less frequently include Cytoxan (also an alkylating agent), Hexamethylmelamine, and 5-Fluorouracil.

Some centres are investigating the role of immune diagnosis and immunotherapy in the management of ovarian cancer. Treatment approaches considered are nonspecific immunotherapy (stimulates immune system), active immunotherapy (tumor cell vaccine), and passive or adoptive immunotherapy.[9]

Because of drug toxicity, personal hardship, and alternate drug regimens available for uncontrolled disease, a further principle in treatment is the second-look surgical procedure which is used for patients clinically in remission after 9 - 18 months of chemotherapy. Laparotomy with multiple biopsies of all areas is necessary to determine if histological disease is absent, in which instance treatment may be stopped.

TABLE VI

5 - YEAR SURVIVAL BY STAGE

STAGE	PERCENT
I	61
(IA	65)
II	40
(IIA	60)
III	5
IV	3

PROGNOSIS

Seventy percent of patients at diagnosis have Stage III or IV disease, which accounts for the poor overall survival rate. Early diagnosis reflects in survival rates.[3] (Table VI)

COMMENT

While many practising family physicians see very few cases of ovarian cancer, the general surgeon may manage a number of the cases in his local setting, and therefore gain considerable exposure to the problem. The population at risk should be screened by pelvic examination to provide early diagnosis. Accurate diagnosis and staging remain the basis for treatment. Removal of ovaries in perimenopausal and post-menopausal patients undergoing pelvic surgery will reduce the incidence of ovarian cancer. □

References

1. **Mattingly R F:** *TeLinde's Operative Gynecology,* 5th ed. Philadelphia, J. B. Lippincott Co., 1977, p. 809-846.
2. **Watring W G, Edinger D D and Anderson B:** Screening and diagnosis in ovarian cancer. *Clin. Obstet. Gynecol.* **22:** 745-758, 1979.
3. **Kistner R W:** *Gynecology,* 3rd ed. Chicago, Year Book Medical Publishers, Inc., 1979, 334-410.
4. **Johnson G H:** Pelvic management and diagnosis of carcinoma of the ovary. *Clin. Obstet. Gynecol.* **22:** 903-923, 1979.
5. **Stern W Z:** Radiology of the ovary. *Obstet. Gynecol. Surv.* **34:** 518-525, 1979.
6. **Morrow C P:** Classification and characteristics of ovarian cancer. *Clin. Obstet. Gynecol.* **22:** 925-937, 1979.
7. **Horton J:** Management of cancer of the ovary. *Clin. Can. Briefs.* Sept. 1979.
8. **Young R C, Fisher R I:** The staging and treatment of epithelial ovarian cancer. *Can. Med. Assoc. J.* **119:** 249-256, 1978.
9. **Ballon S C:** Immunotherapy and immune diagnosis of ovarian cancer. *Clin. Obstet. Gynecol.* **22:** 993-1002, 1979.

Gestational Trophoblastic Disease:

ATLANTIC CANADA UPDATE, 1980

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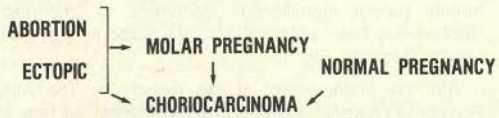
Gestational Trophoblastic Disease includes hydatidiform mole, invasive mole or chorioadenoma destruens, and choriocarcinoma. Their etiology occurs in relation to pregnancy. (Fig. 1)

FIGURE 1

GESTATIONAL TROPHOBLASTIC DISEASE SPECTRUM



The greatest number of cases in any series of gestational trophoblastic disorders consists of hydatidiform mole or molar pregnancy. This disorder may be non-metastatic (most instances) or metastatic. Occasionally from it develops the most lethal form of trophoblastic disease, choriocarcinoma. Whereas most cases of choriocarcinoma and all cases of invasive mole are derived following a molar pregnancy, choriocarcinoma also occurs following a normal pregnancy. This possibility must always be kept in mind when confronted with "reproductive-age" patients, recently pregnant, with unusual signs or symptoms.

Usually, hydatidiform mole is reported by pathologists as "benign". However, approximately 16% of women with this condition will require adjunctive chemotherapy to completely eradicate their disease. This decision is based upon the secretion and subsequent serum values of human chorionic gonadotrophin (HCG) hormone, for it is well known that the HCG levels correlate well with the volume of tumor load. In a few unfortunate instances, where patients have not been followed correctly, significant morbidity and occasional mortality can arise from either non-metastatic or metastatic disease. (Fig. 2). All patients with hydatidiform mole must be followed up to ensure that proper therapy, (when indicated), will not be delayed.

In 1970, this division's first statistics on trophoblastic disease in Nova Scotia was reported in the *Nova Scotia Medical Bulletin*. This comprised a study of 33 patients affected with this condition. In 1977 (also in the *Bulletin*), the reasoning for the establishment of the Trophoblastic Disease Registry and Surveillance Clinic was explained. Our experience in this Clinic concerning the gestational trophoblastic disease 'scene' in the Atlantic Provinces, from 1965 until March 1, 1980 is presented.

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GLOSSARY:

G.T.D — Gestational Trophoblastic Disease
H.C.G. — Human chorionic gonadotropin
N.M.G.T.D. — Non metastatic gestational trophoblastic disease
Chemo Rx — Chemotherapy
Pts — Patients
D & C — Dilation and curettage
T.A. — Therapeutic abortion
M.A. — Missed abortion
Inc. A. — Incomplete abortion
Spont. A. — Spontaneous abortion
HCG — LH — Human chorionic gonadotropin — luteinizing hormone
Pts Req. Rx — Patients requiring therapy
Eval — Evaluation
Dev — Developed
Rx — Treatment
Dx — Diagnosis
Post N pregnancy — post normal pregnancy

CLINICAL MATERIAL

Our total patient load comprises 171 patients. Eighty-three percent or 139 were diagnosed and subsequently confirmed to have a benign hydatidiform mole; 23 patients with hydatidiform mole required adjunctive chemotherapy during their follow-up period to eradicate their disease. These patients represent non-metastatic gestational trophoblastic disease and comprise thirteen percent of our patients. Four percent or 5 patients with molar pregnancies either had initially or subsequently developed during follow-up, metastatic disease. Finally, 4 patients, or 2.3% of the total, presented with choriocarcinoma following a normal pregnancy. One of these, prior to her normal pregnancy, had a hydatidiform mole. (Fig. 3)

From 1965 to 1975, prior to the Trophoblastic Disease Registry being established, we would evaluate 4 to 5 new patients every year. Since the Registry, a gradual annual

FIGURE 2

GESTATIONAL TROPHOBLASTIC DISEASE PROGNOSIS

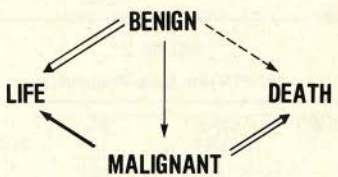


FIGURE 3

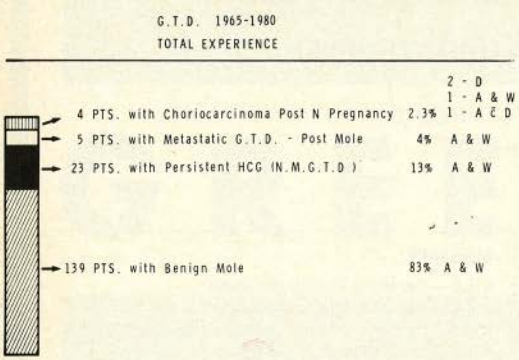


FIGURE 4

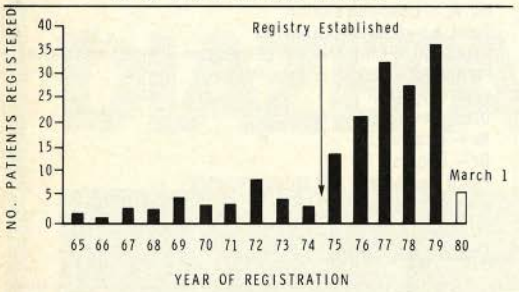


FIGURE 5

Diagnosis Established

Pathology		54/167 or 31 percent	
From D & C For			
T.A.	3	1	
M.A.	14	2	DEV. N.M.G.T.D.
INC. A.	25	4	
SPONT. A.	9		
HYSTERECTOMY	2		
HYSTEROTOMY	1		

8 pts. entered surveillance programme via pathologist reporting.
2 pts. entered surveillance programme via hormone Lab Route.

FIGURE 6

Atlantic Provinces Input
G.T.D. Clinic

	1965-1970	1971-1975	1976-1980 (March 1)
Nova Scotia	13	27	85
New Brunswick	—	8	25
Prince Edward Island	—	—	3
Newfoundland	—	—	10

TOTAL = 171

FIGURE 7

167 PTS with Molar Pregnancy

ULTRASOUND	Positive	37	
	Negative	12	24% Inaccurate
		49	

increase in the number of patients surveyed has occurred until, at the present time, 34 to 40 new patients every year are being added to our Registry and follow-up system. (Fig. 4)

This increase in registered patients has resulted partly because of increased awareness of physicians regarding the need for trophoblastic disease patients to be followed up in a proper manner, and partly because pathologists in the provincial hospital laboratories have been asked to forward the names of patients with trophoblastic disease to the Registry. With this cooperation, we have been able to identify patients with trophoblastic disease not otherwise reported. One-third of our patients with molar pregnancy have been entered on the basis of pathology reports. This we believe is due to the increased number of out-patient procedures being performed for such indications as missed abortion, incomplete abortion, and therapeutic abortion, etc. Finally, the Hormone Laboratory of the Victoria General Hospital has sent us copies of all patients receiving Beta subunit assay for HCG and, upon following up the names on these requisitions, further patient identification pertaining to trophoblastic disease has been obtained and are subsequently entered into the Registry. (Fig. 5)

With the endorsement of this registry by The Atlantic Society of Obstetricians and Gynaecologists, we note from increments of 5 year intervals, that there has been a substantial increase in the number of patients entered from all the Atlantic Provinces from the year 1976 when compared with the years 1965 to 1975. (Fig. 6)

MANAGEMENT

Patients suspected of having a hydatidiform mole pregnancy are eventually diagnosed by means of a clinical history, signs and symptoms, and the spontaneous passage of grape-like material from the uterus or as the result of a diagnostic ultrasound which confirms the molar pregnancy. It is interesting to note that 12 of 49 patients having had ultrasound tests performed were reported as normal pregnancies, yet subsequently, they passed a mole. (Fig. 7) Similarly, one patient was referred with a diagnosis on ultrasound of a molar pregnancy at 8 weeks gestation without any signs and symptoms. Upon repeating the test, a normal pregnancy was found and subsequently a normal fetus delivered. These facts imply that clinical judgement remains the priority in decision making concerning the presence or absence of a molar gestation.

Once the diagnosis of a molar pregnancy has been established, evacuation is carried out, and this is best done utilizing the suction curettage method. A chest x-ray must be obtained to ensure no metastatic lesions are present, and pelvic examination must be thorough to exclude vaginal lesions and/or ovarian enlargement, and theca lutein cysts — the latter related to excessive HCG production. This latter development will regress once the molar pregnancy has been evacuated and the HCG levels return to normal. At the time of uterine evacuation, a separate sample of tissue in close proximity to the uterine endomyometrium should be forwarded to the pathologist for diagnostic purposes. At present, the indications for adjunctive chemotherapy would be the *verified* diagnosis of patients with invasive mole, metastatic mole or choriocarcinoma. In our series 2/167 or 1.2% met these criteria.

FOLLOW-UP

The diagnosis of molar pregnancy having been confirmed pathologically, the patient should now be registered with the Trophoblastic Disease Registry and entererd into the follow-up program. This entails that: 1) the patient be placed on effective contraception; 2) weekly serum samples be forwarded to the Victoria General Hospital Hormone Laboratory for Beta subunit assay, HCG and the requisition be properly labelled with the diagnosis. Eighty-five percent of patients with "benign" molar pregnancy will have their hormone values return to normal within 15 weeks following evacuation. (Fig. 8) The remaining 15% will take a longer time but providing their assay are decreasing, no active intervention is required.

FIGURE 8

Using Urine Quantitative HCG-LH and/or BETA SUB UNIT HCG TITRES
105 pts. with Benign Mole — no sequelae

TITRES
6% are normal < 4 weeks after eval.
35% are normal < 8 weeks after eval.
68% are normal < 12 weeks after eval.
85% are normal < 15 weeks after eval.

15% will take longer (E.G. 23 weeks in one patient).

Similarly, those patients who develop either non-metastatic or metastatic trophoblastic disease following their molar pregnancy, will be identified by prolonged plateauing or rising HCG titers within the same 14 week time interval. (Fig. 9) With this weekly follow-up program, appropriate therapy can be instituted at the *earliest possible time* and *cure* guaranteed.

FIGURE 9

Re 23 Pts with N.M.G.T.D.

20/23 or 80% were identified within 14 weeks of follow up as requiring adjunctive therapy.

2 not entered programme until 24 weeks.

1 in retrospect could have been Rx@ 19 weeks

CHEMOTHERAPY

The incidence of patients requiring chemotherapy to eradicate their persistent trophoblastic tissue in molar pregnancies is reported to be approximately 16%. In our series, from 1965 to 1970, 30% of patients required therapy; from 1971 to 1975, 34% and, with the increasing numbers of patients from 1976 to 1980, 9% required it. There is no way to determine which patients will require chemotherapy on the basis of a pathology report with hydatidiform mole. The Beta subunit assay HCG is a reliable indicator of tumor load. The result of this assay govern the decision to treat or not to treat adjunctively with chemotherapy. (Fig. 10)

RESULTS

In our series of 167 patients with hydatidiform mole, 23 required adjunctive therapy for non-metastatic disease. These patients received from 1 to 4 courses of treatment and all are alive and well.

Five patients with molar pregnancy developed metastatic trophoblastic disease (all pulmonary — one also vaginal); 3 had metastases at the time of diagnosis of their molar pregnancy and were placed on chemotherapy then; 2 patients developed it during their follow-up — diagnosed because of rising HCG titers some weeks following the evacuation of the molar pregnancy. These 5 patients received from 1 to 5 treatment cycles and all remain alive and well.

CHORIOCARCINOMA FOLLOWING NORMAL PREGNANCY

Our experience with choriocarcinoma postnormal pregnancy is similar to others. This is an extremely rare condition and we have seen 4 patients.

Patient 1 was diagnosed at the time of caesarean section, performed because of fetal distress, and she was referred to Halifax within three weeks. The diagnosis having been established, she was treated with combination chemotherapy for 3 cycles and remains alive, well free of disease and off of follow-up.

The remaining 3 patients have all died, either of complications or drug resistant choriocarcinoma. The first of these presented six weeks following vaginal delivery at an outside hospital. A chest x-ray 48 hours post delivery showed multiple pulmonary nodules interpreted as broncho-pneumonia. She subsequently was admitted to the Department of Medicine with hemoptysis, the diagnosis was quickly established and she transferred to Gynaecology, but unfortunately died of tumor resistence in spite of aggressive chemotherapy.

The second patient had complained for some 7 months, following a vaginal delivery, of amenorrhea, fatigue, anemia and was admitted subsequently to the Department of Psychiatry. The diagnosis was suspected on gynecologic consultation. She underwent a laparotomy with jejunal resection, because of gastro-intestinal hemorrhage, and was then started on chemotherapy. She died of a pulmonary embolus five days following surgery.

The final patient had a hydatidiform mole 5 years prior to her last delivery. She presented with hemoptysis 18 months post delivery and was admitted to the Department of Thoracic Surgery. Evaluation revealed a mediastinal mass and surgical attempt at removal was incomplete. The pathology was reported as choriocarcinoma. She was transferred to the Department of Gynecologic Oncology where, after agressive chemotherapy comprising 23 courses of combination drugs, she died of persistent choriocarcinoma with metastases generalized throughout the body.

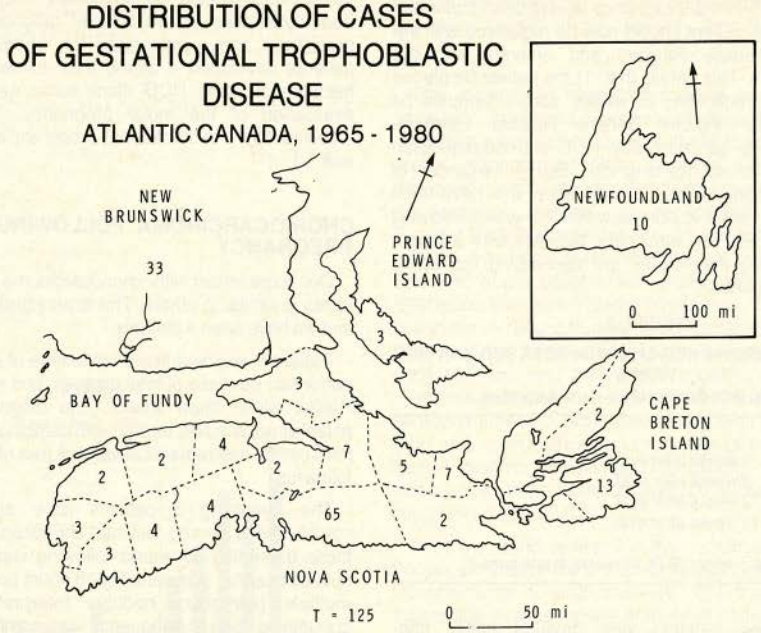
FIGURE 10

% Pts. REQ. Rx — Referred with Dx Molar Pregnancy

	1965-1970	1971-1975	1976-1980
N.S.	4/13	6/27	9/85
N.B.	—	6/8	1/25
P.E.I.	—	—	0/3
NFLD.	—	—	2/10
	30%	34%	9%

% pts. with Mole req. Chemorx = 16.79%

FIGURE 11



These four cases relate the story of choriocarcinoma post normal pregnancy. It is difficult to diagnose unless it is considered. *An HCG assay should be performed on any woman in the reproductive age with a history of normal or abnormal pregnancy and unusual symptoms.* These patients have a greater chance of survival if their diagnosis is established less than 4 months from the preceding pregnancy, at a time when the HCG titer is under 100,000 IU's and before the development of cerebral or hepatic metastases. Sophisticated extensive investigation is required. Surgery is rarely indicated unless as a lifesaving measure and therapy is predominantly with the use of cytotoxic drugs and life support measures. Invariably due to the type of presenting complaints, these women are initially admitted to non-gynecologic services.

CONCLUSION

In Nova Scotia, over the past 15 years, 125 cases of trophoblastic disease have been diagnosed. A survey of all the pathology departments in the province in 1979 revealed that all patients with trophoblastic disease reported that year were registered and actively followed. This disease can have serious sequelae, which can be prevented with proper follow-up. Women affected with hydatidiform mole, invasive mole, choriocarcinoma, must be registered with the Trophoblastic Clinic and in conjunction with that Clinic and their physicians, be ensured of proper follow-up and treatment program.

I would like to thank the physicians, the pathologists, and the personnel in the Hormone Department, for making this Registry what it is today and we hope that in the not too distant future, the same type of program can be more thoroughly instituted in the provinces of New Brunswick, Prince Edward Island and Newfoundland. Interestingly enough, every geographic district in Nova Scotia has had at least one patient entered into the Registry. (Fig. 11). The experience of any individual physician with this disease is not great but with collective registrations, pertinent data and follow-up recommendations are available to all from the Gestational Trophoblastic Disease Clinic. □

The Clinical Prediction of Ovulation

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INTRODUCTION

Data concerning infertility reveal that about one in ten marriages is childless and it is estimated that another 15% of couples either have fewer children or experience longer intervals between pregnancies than is desired. Of those women who are infertile, at least 20% result from an ovulatory defect.

Classically, the physician assessing the ovulatory status of the infertile woman relies on the history, basal body temperature (BBT) records, and on endometrial biopsy.[1-3] The latter procedure has been criticized for being uncomfortable for the patient, expensive and time consuming. Similarly, the inaccuracy of monophasic basal body temperatures, as a predictor of anovulation, has been demonstrated to be as high as 12 to 15%.[4,5]

A simple but reliable method for the determination of ovulation is desired by the family physician. The purpose of this study was to determine the reliability of the history in predicting ovulation compared with endometrial biopsy, and to investigate further the role of basal body temperature.

MATERIALS AND METHODS

Clinical records for 200 female patients, who had visited the Endocrine and Infertility Centre, Grace Maternity Hospital, Halifax, Nova Scotia, were reviewed. These patients ranged in age from 22 to 34 years, with a mean age of 25. The data collected for each patient included infertility status, cycle pattern, premenstrual symptoms, basal body temperature records, and the results of their endometrial biopsy.

TABLE I

Summary of Data For 200 Patients

Fertility	Cycle Pattern	Premenstrual Symptoms	Basal Body Temperature	Endometrial Biopsy Anovulatory	Endometrial Biopsy Ovulatory
Primary	Abnormal	Absent	Monophasic	0	0
			Biphasic	0	0
		Present	Monophasic	1	0
			Biphasic	2	11
	Normal	Absent	Monophasic	0	0
			Biphasic	0	8
		Present	Monophasic	4	1
			Biphasic	1	97
Secondary	Abnormal	Absent	Monophasic	2	0
			Biphasic	0	1
		Present	Monophasic	1	0
			Biphasic	1	8
	Normal	Absent	Monophasic	0	0
			Biphasic	0	4
		Present	Monophasic	0	0
			Biphasic	1	57

Recently, single luteal phase progesterone measurements have been used to indicate ovulation, as an alternate to endometrial biopsy.[6] Using them as a confirmation for ovulation, Magyar *et al.*[5] concluded that regular menstrual cycles, accompanied by premenstrual symptoms, were predictive of ovulation in 80 to 90% of the subjects studied. Unfortunately, these measurements are expensive and not widely available.

Fertility status may be classified as either "primary" or "secondary". Primary infertility is defined as one year of unprotected intercourse with the intention of achieving pregnancy, but without success. The classification of secondary infertility is applied to those patients who have had a previous pregnancy but who have now failed to become pregnant — again, after one year of unprotected intercourse.

Patients were then separated into two groups according to their cycle pattern — "normal" if between 21 and 35 days and "abnormal" if outside this range. Premenstrual symptoms included dysmenorrhoea, mastalgia, bloating, tension

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headaches and cramps, and these were recorded as present or absent. BBT charts, constructed from oral temperature recordings, displayed either a biphasic or monophasic pattern according to the method of Vollman,[1] and were assessed prior to the knowledge of the endometrial biopsy results. Endometrial biopsy reports were available in all cases, and were classified as "ovulatory" or "anovulatory". All biopsy specimens had been examined by one pathologist, Dr. Ismail I. Zayid.

Data were coded appropriately and analysed by BMDP Biomedical Computer Program "P3F (Multiway Frequency Tables — The Log-Linear Model)". The purpose of this analysis is to obtain a description of the relationships between the factors of the table, either by forming a model for the data or by testing and ordering the importance of the interaction between the factors.[7]

RESULTS

Data collected for all 200 patients have been summarized in a multiway frequency table, with the first categorical variable (fertility status) shown horizontally and the other four variables shown vertically (Table I):

Tests of first-order interactions show that no significant association exists between either fertility status ($P = 0.9777$) or premenstrual symptoms ($P = 0.5939$) and the endometrial biopsy results. However, cycle pattern ($P = 0.0073$) and BBT ($P < 0.0001$) are significantly related to the biopsy results. Thus by eliminating the nonspecific information, Table II provides a succinct assessment of the pertinent data.

TABLE II

Cycle Patterns and Basal Body Temperatures Compared With Results of Endometrial Biopsy

Cycle Pattern	Basal Body Temperature	Endometrial Biopsy Anovulatory	Ovulatory
Abnormal	Monophasic	4	0
	Biphasic	3	20
Normal	Monophasic	4	1
	Biphasic	2	166

Because the expected values for some cell frequencies are small, 0.5 was added to each cell and, in succession, several models were fitted to test the effects of various combinations of the factors. That showing the greatest degree of independence between the factors (goodness-of-fit $\chi^2 = 0.35$; $P = 0.8389$) is reproduced in Table III:

TABLE III

Fitted Frequencies For Cycle Patterns, Basal Body Temperatures and Endometrial Biopsy Results

Cycle Pattern	Basal Body Temperature	Endometrial Biopsy Anovulatory	Ovulatory
Abnormal	Monophasic	4.308	.107
	Biphasic	2.692	19.893
Normal	Monophasic	3.692	.893
	Biphasic	2.308	166.107

From this table, it is now possible to predict ovulation by calculating the odds ratios for all combinations of cycle patterns and BBT. For example, if a patient has an "abnormal" cycle pattern and a "biphasic" BBT, then the probability of ovulation is $\frac{19.893}{2.692 + 19.893} = 0.8808$. Expressed as percentages, all four probabilities are shown in Table IV:

TABLE IV

Prediction of Ovulation Based on Basal Body Temperature and Cycle Patterns

Cycle Pattern	Basal Body Temperature	Probability of Ovulation
Abnormal	Monophasic	2.4%
	Biphasic	88.1%
Normal	Monophasic	19.5%
	Biphasic	98.6%

Even considering BBT records in isolation (Table V) provides useful information, for 1 in 9 (or 11.1%) of patients with a "monophasic" BBT will be ovulatory.

TABLE V

Comparison of Basal Body Temperature With Endometrial Biopsy

Basal Body Temperature	Endometrial Biopsy Anovulatory	Ovulatory
Monophasic	8	1
Biphasic	5	186

DISCUSSION

In our study, endometrial biopsy was the confirmatory test used to determine whether patients were ovulatory or anovulatory. From the data collected for each patient, it was found that information about fertility status and premenstrual symptoms do not assist in determining ovulatory status. However, cycle pattern and BBT pattern were significantly related to the outcome of endometrial biopsy.

By examining all possible combinations of these two factors (i.e. cycle pattern and BBT), it was calculated that an "abnormal" cycle pattern and a "monophasic" BBT predicted ovulation in only 2.4% of cases, whereas the same cycle pattern with a "biphasic" BBT predicted ovulation in 88.1%. Similarly, a "normal" cycle pattern with a "monophasic" and with a "biphasic" BBT predicted ovulation in 19.5% and 98.6% of cases, respectively. Therefore, a "biphasic" BBT is the most important single factor in predicting ovulation.

The association found between cycle pattern and ovulation confirms the observations of Magyar *et al.*[5] However, these two studies differ markedly with respect to the role of premenstrual symptoms in the prediction of ovulation. This difference cannot be explained, since data concerning premenstrual symptoms is not presented by Magyar.

The proportion of patients with a "monophasic" BBT and who were nonetheless ovulatory was 11.1%. This compares with 12% in Moghissi's study,[4] and with 30% reported by Magyar *et al.*[5]

CONCLUSION

Because BBT charting is relatively simple, non-invasive and inexpensive, it is a very useful aid for the family physician assessing ovulation. Since information concerning cycle pattern improves the predictive value of BBT, physicians should use both for predicting the ovulatory status of their patients. □

ACKNOWLEDGEMENTS

We are indebted to Dr. J. Barry Garner and to Ms. Lily Rai for their assistance with biostatistical and computing services.

References

1. **Vollman R F:** *The Mernstrual Cycle.* Philadelphia, W. B. Saunders, 1977. Pgs. 74-81, 91.
2. **Speroff L, Glass R H and Kase N G:** *Clinical Gynecologic Endocrinology and Infertility,* Second Edition. Baltimore, Williams and Wilkin, 1978.
3. **Johansson E D B, Larsson-Cohn U and Gemzell C:** Monophasic basal body temperature in ovulatory menstrual cycles. *Am. J. Obst. Gyn.* **113**: 933, 1972.
4. **Moghissi K S**: Accuracy of basal body temperature for ovulation detection. *Fertility and Sterility* **27**: 1415, 1976.
5. **Magyar D M, Boyers S P, Marshall J R and Abraham G E**: Regular menstrual cycles and premenstrual molimina as indicators of ovulation. *Am. J. Obst. Gyn.* **53**: 411, 1979.
6. **Israll R, Mishell D R Jr, Stone S C** *et al:* Single luteal phase serum progesterone assay as an indicator of ovulation. *Am. J. Obst. Gyn.* **112**: 1043, 1972.
7. **Brown M B**, Editor. *Biomedical Computer Program Series.* Berkeley, University of California Press, 1979. Pg. 297 *et seq.*

An Outline of Reproductive Care in Nova Scotia

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The following report is a clarification of The Medical Society of Nova Scotia's "Prenatal Care Programs . . ." report in the *CMA Journal*/December 22, 1979/Volume 121.

Since 1959, when The Medical Society of Nova Scotia's Committee on Maternal and Perinatal Health was formed, perinatal mortality in this province has fallen by 54%, and in 1977 was the lowest in Canada.[1] Perinatal mortality over 1000 grams and less than 7 days (the latest WHO definition) was also low, at 10.52 per 1000 in 1978, with neonatal mortality 3.98** per 1000 livebirths. At the same time maternal deaths have virtually ceased.

This progression of Nova Scotia from one of the highest mortality provinces to the lowest is the result of a combination of many interrelated factors. One major factor is the Reproductive Care Program of Nova Scotia with its endorsement by the Medical Society and its continued and enthusiastic support by the Department of Health. Further factors are the work of the three Central Referral Hospital staffs (I.W.K. Hospital for Children, Grace Maternity Hospital and St. Rita's Hospital in Sydney), the supportive response of the 37 other hospital staffs in the province, the excellent antenatal care and services provided by the Department of Health in the province, as well as the Nova Scotia Fetal Risk Project under the direction of Dr. Michael Hebb.

The Reproductive Care Program (R.C.P.) was begun in 1973.[2] The most important component of this program is the Obstetrical-Neonatal Nurse Visiting Program provided to all hospitals in the province. The two nurses have made 183 visits, have worked in each hospital for up to a week at a time, teaching the practical aspects of obstetrical and neonatal nursing care on a one-to-one basis and in groups and seminars. In addition, 58 nurses have taken the postgraduate maternity and neonatal courses. The R.C.P. central office with the Action Group functions to organize and administer the program, and to maintain communications.

In addition, periodic on-site perinatal reviews of hospital charts are carried out with the survey results presented to the medical staff of each hospital reviewed. Individual physicians are also asked to complete and send a report on each of their perinatal deaths to the central office. High Risk Rounds, informal presentations of perinatal patient management problems to members of hospital staff, with participation by members of the R.C.P. Action Group, take place at regional hospitals. Data collection and analysis, with feedback of interpretation and suggestions, is carried out.

This program is voluntary, is endorsed by the Medical Society, and is supported by the Department of Health. The responsibility for improvements in perinatal care remains that of the physicians, nurses and staff of the community and regional hospitals, and the Branch Medical Societies.

R.C.P. Action Group	N.S. Committee on Perinatal Health
A. Allen	
J. Buckley	
M. Hebb	A. Allen
J. MacDonald	M. Hebb
M. Muise	R. E. Lea, Chairman
N. Nelson	L. Peddle
L. Peddle	K. Scott
E. Rees	E. Rees
K. Scott	
N. Ryley Tuckett	
W. Woodhams	

Bibliography

1. Annual Report of the Registrar General, Province of Nova Scotia, for the year ending December 31st, 1972. Queen's Printer, Halifax.
2. Proceedings of the National Conference on Prevention and Social Policy, Winnipeg, Manitoba, October 21-23, 1979.

*Neonatal Co-Director, Reproductive Care Program.

**1000 grams or greater, less than 7 days.

The Community Hospital and the Terminally Ill

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"It is dying, not death that I fear"

—Montaigne

DEATH AND SOCIETY

Over the past decade there has been a growing interest in thanatology and a greater research in the process of dying, but society still has a tendency to focus on youth, beauty and success, and to individually and collectively deny the facts of dying and death.[1]

This is particularly so in many hospitals where dying patients are sometimes moved to a private room away from others; where staff still feel uncomfortable in the presence of the dying and, helplessly, often do not know what to do or say. Dying patients may feel so abandoned by their families, deserted by their physicians, and avoided by their nurses to a point of depersonalization and isolation. Therefore, they cannot communicate their feelings, frustration and expectations about dying to be able to die with dignity, courage, in peace and comfort.

Once upon a time, death was a natural event in society. Birth, life, and death were shared events which occurred in the home environment, supported by family, friends and neighbors. Death was viewed as part of life, happening every day and looked upon in the context of nature with it's cycle of life and death as something normal and to be expected.

In time, the process of dying became a social problem and remains so to a great extent. This denial of death or frustration of death in our technological society has resulted from a number of factors. First, over the years, the medical profession has become successful in eliminating many communicable diseases and other disease conditions, thereby changing mortality statistics from early death to increased longevity, with a resultant aging population and an increase in chronic long term diseases. Added to this, new techniques and therapeutic procedures tend to lengthen the time between the onset of a terminal illness and death, prolonging the agony and suffering of both patients and families and, also, posing many moral and ethical issues. Medical education is such that there is emphasis on the prolongation of life to the extent that to many physicians, death is viewed as a "therapeutic failure".

Other contributing factors include the demise of the extended family, leaving most people helpless to cope with the needs of patients whose health cannot be restored. Many families live in apartments or small homes with little room for a terminally ill relative.

Death is a social fact, real and inescapable. Although it poses a terrifying threat to the realities of everyday life that are taken for granted, nonetheless, it is inevitable. When the acceptance is realized by patients, families, and certain other persons, the particular stigma associated with dying can be eliminated and death appears less threatening to all concerned. It is most unlikely that we will ever return to the 'good old days' when people died peacefully at home surrounded by their loved ones, when having a good death was considered an important part of living the good life.

However, there is a growing new institution in its developmental stage both in the United States and in Canada, i.e., the hospice, with its major goal to provide supportive care to the dying patient and their families in an atmosphere as homelike as possible. The hospice concept, patterned after the work of Cecily Saunders of Great Britain, stresses the individuality of each patient and continued support from family and friends in a warm open atmosphere, improving the quality of life for as long as possible.

At the present time there are only a few free standing hospice centres, functioning independently of general hospitals in the United States and Canada. In Canada, there is only one such hospice in Ontario, the Salvation Army Hospital, officially opened last June. There are several palliative care units located in general hospitals and there are at least three such units in Canada.

One must consider that the majority of terminally ill usually die in hospitals and institutions. These hospitals may be tertiary, regional or community, places often equipped with massive and complex technology capable of supporting life — active treatment centres when cures are no longer possible, so that many will die under less than ideal circumstances. There is a great need for community hospitals to improve their care of the dying and the need for hospice care becomes very clear.

However, due to increased costs of health care, the community hospitals are forced to provide active treatment and, frequently, long term patients and terminally ill patients are compelled to find alternate accommodations in the community. As stated previously, modern society has rejected the idea of keeping the terminally ill patient at home so that the dying patient is admitted to the hospital, often much earlier than is sometimes necessary. This presents a significant gap in our health care system, as acute care hospitals are geared to focus on investigation, diagnosis and cure, whereas terminally ill patients require much medical, nursing and supportive care, which most often can only be provided in a hospital environment.

Therefore, the community hospital must define the patient's needs, depending on the patient's physical and mental status. The care of the terminally ill requires a multidisciplinary approach from physicians, nurses, social workers, volunteers, and other community resources, including family, friends and Pastoral Care Services depending upon the individual. Multidisciplinary, because no one person can fully meet the needs of the dying patient for their needs and those of their families are complex, demanding and draining. The patient and family should be integral members of the health care team, and the family included as "givers" of care as much as possible. Similar services should be

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extended to the dying patients who choose, or have chosen for them by the physician or family, to remain at home during their terminal illness. These services should be properly co-ordinated in the appropriate manner as provided in the community hospital.

The community hospital should develop liaison with the regional and tertiary care hospitals, nursing homes, home for the aged where frequently patients are transferred respectively during certain specific stages of their illness and from where they are returned to the community hospital for continuation of their care. Ideally, the community hospital should designate an area where terminally ill patients can be cared for with maximum comfort. There should be total provision of medical, nursing, and supportive services including pastoral care and the other community resources that could be brought to the patient in the community hospital. Such an area could be called a palliative care or terminal care unit.

However, if the community hospital is unable to develop this type of unit in the institution, the concept of hospice care can still be carried out, integrated into the mainstream of medicine, nursing and supportive care in the general community hospital. Realistically, it is not feasible to build, operate and staff enough free standing hospices to begin to satisfy the need. Due to lack of bed space and sometimes because it is costly to give good hospice care, and because of the high ratio of staff to patients, it is also not feasible to establish palliative care units in community hospitals.

Hospice care which is simply good medical patient care, can be fused into the medical and supportive services and given in a general hospital. The outstanding feature includes compassion, emotional security, and loving care given around the clock, tailored to anticipate the unspoken needs of the patients. This kind of human concern, emphasized in hospice care, should really be a part of the framework of all care given in the general hospital.

Hospice is defined as "a program which provides palliative and supportive care for terminally ill patients and their families, either directly or on a consulting basis with the patient's physician or another community agency such as a visiting nursing association."[2] In the light of this definition, hospice care can be given in a general hospital or at home, providing that the care givers are educated to an understanding of the major philosophical differences from the conventionally practiced health care involving the dying. Added to this, the realization when the time comes that further treatment will no longer significantly affect the disease or when the side effects of active treatment becomes more negative offsetting its benefits, and it has been determined that hospice care is more appropriate, the whole approach to care must shift emphasis.

With hospice care, the emphasis should shift to these positive philosophical approaches:[3]

1. Viewing death and accepting death as part of the life cycle.
2. Facing the reality of the situation in consideration of appropriate therapy, i.e., "not shortening life but also not prolonging dying".
3. Emphasis on the details of total care, i.e., skilled symptomatic medical care, expert "bedside" nursing care and a multidisciplinary approach — people oriented and patient centered.
4. Emphasis on the quality of remaining life rather than quantity.
5. Emphasis on opportunity — realizing that there is always much that can and should be done to relieve pain, distress, fear, and isolation. It should be recognized that this could be a period of growth for patient, family and staff.
6. Emphasis on communication and support from nurses, staff, families and volunteers. Unlimited visiting hours and children should be permitted to visit, and families encouraged to stay overnight in crisis periods. The importance of non-verbal (silence and touch) as well as verbal communications, more openness in our discussion of ethical issues, in treatment alternatives and quality of care.
7. Encourage patients and families to share as they wish, to face the reality, to plan the death rituals, to plan the family's future, to proceed with "unfinished business" and indeed to participate in preparatory grief.
8. All aggressive therapy and routine hospital procedures should be discontinued and primary concerns should be those that relate to contributing to the comfort of the patient, mobility and participation, to improving the "quality of remaining life".
9. Treatment should be symptomatic only, such as nerve blocks for relief of pain or oxygen administration to ease breathing, not to prolong life.
10. Major emphasis on *pain control.* Careful and continued titration of the amount of narcotic to individual needs prescribed for administration *around the clock* to eliminate pain and the fear of recurring pain. "Chronic unremitting pain becomes a dehumanizing nightmare." Emphasis on the relief of side effects of narcotics, especially nausea and constipation.
11. Emphasis on the patient remaining at home and dying at home if the patient wishes and if possible. Supportive home care should be given by a multidisciplinary team, 24 hours a day, 7 days a week.
12. Continuity of care so that the patient does not feel abandoned. Staff should be assigned consistently to the same patient as much as possible. Medical and family problems should be sorted out by members of the multidisciplinary team, with the patient and family participating and conferring together as often as necessary.
13. The patient's opinion should be invited and the patient encouraged to participate and contribute to the knowledge and understanding of staff and family for as long as possible.
14. The patient's feelings of self-worth and well being should be encouraged. Diversional and recreational therapy such as physical, occupational, music, etc. should be employed for as long as possible.
15. There should be emphasis on the patient as a person, encouraging the patient to express individuality, e.g., to wear own clothes, to maintain a good body image. The patient should not be expected to fit into a system and follow strict regulations, in other words, allowed to die as he or she has lived.

16. There should be consideration of spiritual matters which should be encouraged, but not forced. Openness and acceptance of patients "where they are", realizing that all staff can participate, not clergy alone; keeping in mind that all are team members.
17. At the time of death, the family should be encouraged to be with the patient, to stay with the body, and time allowed to express emotions or to pray, etc. until the family is comfortable about leaving.
18. There should be more continuing education for all staff involved in the care of the terminally ill in order to recognize the unique needs of the terminally ill. Planned team meetings should take place so that staff feels supported and better able to cope with terminal illness and its related stress and consequences.
19. There should be a Bereavement Follow-Up Program so that team members can provide continued support to the family, to facilitate grief and to identify serious coping problems. Staff attendance at funeral to maintain contact with family would be very significant.
20. There should be a widespread, multidisciplinary education program for professional staff, for students and the public in the philosophy and practice of hospice care. Initially, research and evaluation of patient needs, all aspects of care, medical, social, psychological, spiritual and financial should be carried out. An analysis of alternative structures and financial coverage should be done.

IN SUMMARY

In providing care to the terminally ill in the community hospital, one must keep in mind the concept change in approach and emphasis in care and also the major components of hospice care, i.e. .,

1. Home care in as much as possible, for as long as possible.

2. In-patient care when symptoms cannot be controlled at home, when there is no primary care giver at home or when the primary care giver or the patient is temporarily unable to cope at home.

The major needs of the dying patient providing palliative and supportive care and utilizing the hospice concept can be met in a community hospital; so that the dying can be helped to live their days fully to the very end and we may no longer wonder why many today would say with Montaigne, *"It is dying not death that I fear"* but rather there would be acceptance and assurance that

"To die is an act of life,
As we do not live alone
neither do we die alone".[4] □

References

1. **Germain Carol:** *The Cancer Unit:* An Ethnography. Nursing Resources, Inc. 1979, p. 11.
2. **English David and Wilson Dottie:** *Hospice Concept,* Elm Services Inc. 1979, p. 3.
3. idem, p. 4-6.
4. **Roy David J:** How To Care When We Cannot Cure, *Can. Med. Assoc. J.* **120:** 1282, 1979.

The Management of Psoriasis in Maritime Canada

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Psoriasis affects approximately 2% of the population, and it is estimated that approximately one per thousand of the population seek doctors' help at any given time. Our centre serves approximately 1.3 million population from the three Maritime Provinces and hence we would expect approximately 1300 patients seeking help on a regular basis from the doctors in the area. This is not an inconsiderable number of patients. Considering the medical implications of psoriasis being a disease that is life-spoiling to life-ruining, the condition rates high priority of attention of family doctors and dermatologists.

Psoriasis has been well-reviewed recently[1-4]. The chapter by Farber and Van Scott[5] is a useful summary.

MANAGEMENT OF PSORIASIS

In managing any patient for the first time, detailed explanation of the nature of psoriasis in terms that are easily understandable, is essential. One useful method is the comparison of the disorder to a physiological type of birthmark, the patient being told that he or she has been born with an innate tendency to have psoriasis; that outbreaks can be provoked throughout lifetime by a variety of stimuli external or internal a few of which only are understood and the majority not understood. The patient is told that despite all this, medicine can offer several types of treatment the aim of which is to clear the patient completely and thus give the longest period of remission. The principles that guide such treatment are that the treatment be economical, easy to use, acceptable and provides the longest remission possible to achieve.

Medically supervised treatment is delivered in three ways. The majority of patients are treated under supervision from the physician's office. The frequency of visits would depend upon the condition and regimen of treatment being used. If treatment with Anthralin is being prescribed for the first time, it may be wise to review the patient after three or four days so that anticipated side effects can be explained. A further review might be made at one week to decide if the strength of paste needs to be changed. Thereafter patients would be reviewed at four and six week intervals, bearing in mind the normal pace of response treatment. If tar is chosen as the initial treatment, the first review would be held at a longer interval of time such as three or four weeks and followup reviews would likely be at monthly intervals.

Daily Outpatient Treatment

For the patient who has fairly extensive psoriasis and might need Ingram's Anthralin paste treatment for the first time or the Goeckerman regimen of treatment, daily outpatient treatment under the supervision of a skilled nurse with physician's direction might well be the choice. Such a clinic has been established in the Outpatient Department at the Victoria General Hospital attended by dermatologists. Ideally the patients should live fairly close to the centre so that there is minimum interruption of the working day schedule. If not and, if it is not necessary that the patient be admitted, the Government of Nova Scotia now funds hostel accommodation and meals nearby. If a patient is failing to respond to supervised treatment from the office, then daily outpatient treatment provides the opportunity for skilled supervision. The Ingram regimen is the one most commonly used in the Halifax daily outpatient treatment and ideally the whole treatment process takes one hour to complete. Appointments are made as flexible as possible so that the patient's working day is interfered with the least.

Whether treatment takes place from the office, daily outpatients' or as inpatient, education of the patient is of the greatest importance. The opportunities for contact between patients and the intimate contact with nursing staff makes the hospital the best setting for learning about psoriasis and its management. The patient must understand the nature of the disease process, the techniques of treatment and dressing, the various strengths of application, the methods of storage and renewal and above all the necessity to treat any recurrence of the disorder aggressively as soon as it occurs.

Inpatient Treatment

In Halifax, ten beds are currently assigned for the treatment of dermatologic patients and they are situated at the Victoria General Hospital. The majority of beds are usually occupied by psoriatic patients coming mainly from Nova Scotia, New Brunswick and Prince Edward Island, with a few patients from Newfoundland and even more distant provinces. The ward has its separate ultraviolet ray room, modified bath and treatment room close by. Inpatient admission is indicated for those who are ill or infirm and have psoriasis, those patients who have very inflamed and extensive psoriasis or those requiring special investigation. The mean treatment time is identical to that of outpatients being approximately 18 days with a few patients clear about 14 or 15 days and some taking up to approximately 30 days.

Use of Tar

Tar is keratolytic, has an anti-eczematous and anti-psoriatic action as well as being anti-pruritic. Coal tar is used mainly although a variety of wood tars are available if the patient is intolerant of coal tar. Used in the bath, coal tar solution renders the patient more sensitive to ultraviolet ray. A variety of preparations are available in scalp, lotion, cream and paste bases, the choice depending on the area to be treated. Some standard formulations used locally are listed in the Dalhousie Formulary[6].

Tar preparations are useful in the treatment of acute guttate psoriasis, the so-called geographic pattern of

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psoriasis, erythematous psoriasis with barely palpable plaques and also for clearing the scaling and staining after treatment with Anthralin preparations.

There are various modifications of the classic Goeckerman regimen[7]. In the regimen used locally, White's tar paste D.F. is applied to the whole body with the exception of the face and covered with a stockingette suit. After 24 hours the excess is removed with mineral oil, the patient exposed to increasing sub-erythema doses of ultraviolet ray, given a tar bath and the White's tar paste replaced. Triamcinolone 0.1% ointment or cream can be used sparingly about the face and genital area and tar pomade D.F. about the scalp. In normal clinical practice the long term risk of inducing skin carcinoma with such regimens is negligible[8].

The smaller type of ultraviolet ray lamp, purchased for use in the home, is useful for tte cosmetic effect of tanning but has no beneficial anti-psoriatic action. The energy output and action spectrum is different to that of the hospital-type ultraviolet ray which has a much greater energy consumption.

Anthralin

Anthralin (Dithranol in the United Kingdom and Europe) is the active principle of Chrysarobin, an extract of goa bark which was in popular use incorporated as an ointment until the 1930's. The Ingram regimen consists of a daily tar bath, followed by whole body ultraviolet ray and the application of Anthralin in strengths ranging from 0.1 to 0.4% in paste base. Scalp preparations are available. Details of application are reviewed by Comaish[9] and Ross[10].

The addition of the tar bath and ultraviolet ray are used in outpatient and inpatient treatment only, as they are believed to hasten recovery slightly. These additions are unnecessary in home use. Old underclothing, pyjamas, etc. can be modified as dressings for use in the home.

Topical Corticosteroids

These agents have only a limited role in psoriasis, and the uses and side-effects have been reviewed recently for Maritime practitioners[11]. In general, mid-potency fluorinated corticosteroid preparations can be used about the face, flexural and genital areas for a period of a few weeks, coincidental with the use of tar or Anthralin. Plaques of psoriasis that are responding poorly to treatment with non-steroid agents, may be made to respond by occlusion with most potent topical Corticosteroid agents, applied for three of four times for periods of 12 hours under plastic occlusion at 24-hour intervals.

If topical corticosteroids are used extensively for long periods of time on psoriasis, they not only render the condition refractory to other treatments for several weeks after withdrawal but may, in addition, make the patient's skin atrophic, and be absorbed to the extent of making the patient cushingoid (Clobetasol Valerate) and, in withdrawal, produce generalized pustular psoriasis[12]. Despite this, recurrent patches on areas such as the genitalia can be treated with intermittent short courses of medium potency fluorinated corticosteroids. Small patches of psoriasis obstinate to treatment in areas where difficulty can be anticipated such as the palms and soles, can be cleared occasionally with injections of intralesional corticosteriod.

Grenz Ray Treatment

Grenz rays are low kilovoltage x-rays generated at 10 Kv through a beryllium window. They have very superficial penetration and, compared with more conventional superficial x-ray generated at 50 to 60 Kv, have a much greater dosage latitude, A patient may receive up to 8,000 Rads in a lifetime but, an effective dosage to a plaque of psoriasis might be three applications of 200 Rads at seven to fourteen day intervals. This is alternative treatment available for small areas of psoriasis not responsive to topical treatment and is available in the Halifax area to dermatologists on referral to the Radiotherapy Department.

Oral Treatment of Psoriasis

For patients who have life-ruining psoriasis and who have suffered extensive relapses on at least two occasions within a few weeks or at the most one or two months after having received a minimum of two courses of orthodox treatment — Goeckerman or Ingram regimens, Methotrexate is an alternative. The guidelines endorsed by the American Academy of Dermatology are described by Roenigk *et al.*[13] Patients who are diabetic or cirrhotic are excluded. Alcohol should not be taken whilst consuming Methotrexate. As a preliminary, all paitents should have a liver biopsy. Liver function tests are only of value in excluding gross liver damage and minor fluctuations of liver enzymes that may be noted are of no consequence. The dosage is 0.2 to 0.4 mg/kg and is given either as a single dose once weekly or in a reduced amount in three equally divided doses at 12-hourly intervals once weekly when the patient's condition is stabilized. The dosage is tailored to that which just controls the psoriasis. Liver biopsy is mandatory on a yearly basis. The patient should be followed by a dermatologist or physician with special experience in the use of the drug. If the guidelines are followed the majority of patients can take the drug without any complication. There is considerable experience of patients who have taken this drug for 20 years continuously and who have had no adverse side-effects.[14] Alternative medications for those whose condition is unaffected by Methotrexate or who cannot take the drug are Hydroxyurea and Mycophenolic acid.

Hydroxyurea is available in Canada, and it is manufactured by Squibb.[15] as Hydrea. It has no hepatotoxicity although it has a gradual marrow suppressive effect. The response to treatment is slow, and it is approximately three months before reasonable effect is seen. The dosage is 0.5 g b.i.d. to t.i.d. and should be adjusted so that the total white count does not fall below the 3,000 cells per cu. mm.

Mycophenolic acid is available in the United States made by Lilly. It has not been used in Maritime Canada.

PUVA (Psoralen Ultraviolet light A treatment) is a useful alternative treatment for patients with difficult recurrent psoriasis who have failed with or are not candidates for oral therapy and who live within reasonable access to the delivery of treatment. Its use, indications and contraindications are detailed in the accompanying paper by Elliott[16]. One PUVA machine has recently been installed in the Dermatology Outpatient Department at the Victoria General Hospital in Halifax for whole body use and a machine for regional use has been constructed.

CONCLUSIONS

With the many means of treatment of psoriasis available and with the generally good response, physicians should preserve an optimistic outlook in relation to the management of the disorder and this should be conveyed to the patient. All physicians should have a knowledge of the various means of treatment and make these available to patients as is deemed appropriate. □

References

1. **Baker H: Psoriasis: a review,** *Dermatologica* **150:** 16-25, 136-153, 1975.
2. **Baker H,** *et al: Psoriasis, Recent Advances in Dermatology.* Edited by A. Rook, Edinburgh, Churchill Livingston, 1973.
3. **Farber E M and Cox A J** (eds): Psoriasis: proceedings of the International Symposium, Stanford University, Stanford, California Univ Press, 1971.
4. **Faber E M and Cox A J** (eds): Psoriasis, proceedings of the Second International Symposium, New York, York Medical Books, 1977.
5. **Farber E M and Van Scott E J:** *Dermatology in General Medicine.* Fitzpatrick T B et al. Chapter 26, pps. 233-247. 2nd ed. McGraw-Hill, Inc., 1979.
6. Dermatology Formulary of Topical Preparations, 2nd ed. 1978 Dalhousie University and Associated Hospitals, Halifax, N.S.
7. **Goeckerman W H:** The treatment of psoriasis, *Northwest Med.* **24:** 229-231, 1925.
8. **Stern R S, Zierler S and Parrish J A:** Skin carcinoma in patients with psoriasis treated with topical tar and artifical ultraviolet radiation, *Lancet* **i**: 732-735, 1980.
9. **Comaish S:** Ingram method of treating psoriasis, *Arch. Dermatol.* **92**, 56-58, 1965.
10. **Ross J B:** Psoriasis — the Ingram method of treatment, *Cutis* **5**: 1261-1265, 1969.
11. **Klotz J and Ross J B:** Steroids and the skin, *Drugs and Therapeutics for Maritime Practitioners,* **I**:17-20, 1978.
12. **Boxley J D, Dawber R P R and Summerly R:** Generalized pustular psoriasis on withdrawal of clobetasol propionate ointment, *Brit. Med. J.* **ii**:255-256, 1975.
13. **Roenigk H H** *et al*: Methotrexate therapy for psoriasis: Guideline revisions, *Arch. Dermatol.* **108:**35, 1973.
14. **Rook A, Wilkinson D S and Ebling F J G:** Textbook of Dermatology, Blackwell Scientific Publications, 3rd ed. pps. 1343-1346, 1979.
15. **Rook A. Wilkinson D S and Ebling F J G:** Textbook of Dermatology. Blackwell Scientific Publications, 3rd ed. p. 1346, 1979.
16. **Elliott T:** PUVA: Its role in the treatment of psoriasis and other disorders of the skin. *N.S. Med Bull.* **59:** 128, 1980.

PUVA: Its Role in the Treatment of Psoriasis and Other Disorders of the Skin

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INTRODUCTION

It is estimated that some 2,000,000 to 8,000,000 people in the United States alone suffer from psoriasis, a disease of epidermal cell proliferation.[1] The present evidence indicates that it is an inherited disease mediated by multiple genes, although environmental factors are also important for its clinical appearance.[2,3] Psoriasis presents in many forms[4,5] varying in severity from a mild localized scaling to the severe and even life-threatening generalized pustular form with systemic effects.[5] The cost in terms of hospitalization, outpatient and physician fees, and drugs — both prescription and over-the-counter — amounts to $248 million per year.[7]

Many systemic and topical drugs have been used with varying degrees of success in the treatment of psoriasis.[8-10] Since ancient times, however, ultraviolet (UV) radiation has played a major role in the control of the disease. Heliotherapy — the therapeutic use of sun baths — is the earliest recorded treatment and is still in use today.[11-13] The major therapy for much of this century has been the combination of topical crude coal tar or coal tar extracts with UV radiation — the Goeckerman regimen.[14,15] More recently, the combination of anthralin (dithranol) paste, tar baths, and UV radiation — the Ingram regimen — has been an extensively utilized treatment.[16]

The most recent major new therapy for psoriasis involves the ingestion of a photoactive drug, a psoralen (P), followed by whole-body irradiation with high-intensity long-wave UV radiation (UVA) and is thus called PUVA.[1] Although large-scale cooperative clinical trials have repeatedly demonstrated the remarkable efficacy of this treatment,[17-19] and side effects have been almost entirely mild and transient in nature, the treatment is experimental and as yet has not received FDA approval.[20] There is concern that potentially carcinogenic effects of PUVA may not be manifested for many years, as was the case with superficial X-ray therapy.[21] This paper reviews the literature on PUVA therapy in order to evaluate the risk/benefit ratio of PUVA and its role in the treatment of psoriasis and other disorders of the skin.

History

Psoralens are found in over thirty species of plants and have been used medicinally as long ago as 1500 B.C. in India.[22] In the 13th century, Ibn El Bitar described the treatment of *baras* (vitiligo) with the powdered seeds of *Ammi majus*, a psoralen-rich plant, combined with sun baths.[23] In the 1940's, El Mofty[24] isolated several psoralens from this plant and reported success in the treatment of vitiligo with one extract, 8-methoxypsoralen (8-MOP) and either sunlight or UV lamps. In 1960, Becker[25] proposed the use of psoralens in other dermatological disorders that sometimes respond well to sunlight, such as psoriasis. Walter *et al*[26] and Weber[27] reported the improvement of psoriasis using topical 8-MOP and black light. Then, in 1974, Parrish *et al*[1] reported dramatic results with orally administered 8-MOP and UVA: 21 patients with moderately severe generalized psoriasis were completely cleared of psoriatic lesions. Since 1974, the number of PUVA trials has increased steadily and, in 1978, an estimated 35,000 people in the United States alone were receiving PUVA therapy.[28] PUVA has also been applied with success to the treatment of mycosis fungoides,[19,29-36] lichen planus,[36,37] urticaria pigmentosa,[38] atopic eczema,[38,40] erythrodermic seborrhoic dermatitius,[41] alopecia areata,[42] and vitiligo.[19,43-45]

GLOSSARY:

ANA — Antinuclear antibody
DNA — Deoxyribonucleic acid
MF — Mycosis fungoides
5-MOP — 5-methoxypsoralen
8-MOP — 8-methoxypsoralen
MPD — Minimum phototoxicity dose
PG — Prostaglandin
PHA — Photohemagglutinine
PPI — Photosensitivity-pigmentation index
PUVA — Psoralen-long-wave-ultraviolet therapy
SCE — Sister-chromatid exchange
SLE — Systemic lupus erythematosus
UV — Ultraviolet
UVA — Long-wave ultraviolet
UVB — Short-wave ultraviolet

TECHNIQUE

Screening

Because of its experimental status and potential for carcinogenicity, PUVA is for use only in patients with severe or debilitating psoriatic involvement who have failed to improve with conventional therapy.[20,46] PUVA is contraindicated in those patients with a history of photosensitivity or of melanoma.[18,46,47] Indications and contraindications are outlined in Tables I and II respectively.

TABLE I

Indications for PUVA Therapy for Psoriasis[46]

Psoriatic involvement of more than 30% of the body surface
Plaque, localized pustular, von Zumbusch, or erythrodermic psoriasis
Debilitating involvement of the palms and/or soles
Patients in whom methotrexate is contraindicated
Patients who have failed to respond to conventional therapies
Patients with access to PUVA-equipped clinics

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TABLE II

Contraindications for PUVA Therapy for Psoriasis[46-49]

Melanoma or history of melanoma
Photosensitivity
Aphakia or cataracts
Liver damage
Severe cardiac disease*
Old or weak patients*
Less than 12 years of age
Pregnancy†
Use of photosensitizing drugs
Use of systemic cytotoxic drugs less than one month prior to beginning PUVA
Use of other topical or systemic medications during therapy other than emollients

*Unable to withstand the heat of the PUVA chamber
†Precautions to prevent pregnancy should be used during therapy.

Drug Dosimetry

The psoralen is delivered as 10 mg 8-MOP capsules in a single dose calculated on a mg/kg body weight basis as indicated in Table III (after Lynch *et al*[46]). Slightly different dose formulas are also used.[50] A delay of one to two hours follows ingestion of the drug before irradiation as photosensitivity is proportional to the serum level of 8-MOP which peaks between one-half to two hours after oral ingestion.[51] Wagner *et al*[52] found that 8-MOP plasma levels rise significantly slower and remain lower in PUVA-resistant patients compared to PUVA-responsive patients, and that adjustment of the UVA irradiation time to coincide with peak plasma levels led to improvement of the resistant patients.

TABLE III

8-MOP Dosage Schedule for Puva

Body weight	8-MOP
Up to 30 kg	10 mg
30-50 kg	20 mg
51-65 kg	30 mg
66-80 kg	40 mg
81-90 kg	50 mg
91-115 kg	60 mg
115+ kg	70 mg

UVA Dosimetry

The determination of patient photosensitivity is probably the most essential factor of UVA dosimetry. The skin type is classified as in Table IV (after Lynch *et al*[46]). The minimal phototoxicity dose (MPD) is established by irradiating several test fields of skin which is not normally exposed to sunlight with a range of UVA doses (measured in Joules/cm^2) one to two hours after 8-MOP ingestion. The range of doses is determined by the skin type. That dose of UVA which produces a just barely perceptible well-defined erythema is the MPD and is the initial dose for therapy. The readings are made 72 hours after irradiation as this is the time it takes for the phototoxic erythema to develop.[53]

It is also of value to determine the photosensitivity-pigmentation index (PPI) which is the ratio of erythema to pigmentation induced in the test areas of skin. The PPI is an indication of how well the patient will develop tolerance to UVA by pigmentation and serves as a guide to how liberally radiation dose increments during treatment may be made.[53]

TABLE IV

Classification of Skin Type

Type	Characteristics
I	Always burns; never tans
II	Always burns; sometimes tans
III	Sometimes burns; always tans
IV	Always tans never burns
V	Dark-skinned peoples
VI	Blacks

Pohl *et al*[54] demonstrated that provided the dose of 8-MOP is constant, the total amount of UVA determines PUVA phototoxicity, no matter to what extent the dose of radiation is split. Provided the degree of cutaneous absorption is known, then, the total dose of UVA is a valid measure of phototoxicity. However, determining how much UVA reaches the body surface is a difficult task. There are three major factors to be considered in measuring the phototoxic dose of UVA in PUVA therapy: 1) the action spectrum of the psoralen, 2) the emission spectrum of the UVA source, and 3) the spectral response of the UV detector.

The action spectrum of the psoralen is that range of UV wavelengths which photoactivate the drug to produce clearing of the psoriatic lesions, and is usually reported as 320-400nm with a peak at 365nm[46] although other determinations vary.[55] The emission spectrum of the UVA source is the range and relative intensities of the UV wavelenghts it emits and ideally should coincide with the action spectrum for the greatest therapeutic effect with the least UV exposure to the patient.[55] The solid state UV detectors employed in many PUVA radiation chambers are wavelength dependent (they have different detection efficiencies at different wavelengths).[55] Ideally, the spectral response of the detector — the wavelengths to which it is sensitive and the relative sensitivity to each wavelength — should approximate the action and emission spectra.

If there is mismatching between the action spectrum, the emission spectrum and the detector's spectral response, the UVA dosage determination will be inaccurate. Because the action specturm is uncertain, the emission spectrum of UV bulbs alters over the life of the bulb[55] and dosimeter response is typically wavelength dependent, PUVA UVA dosimetry is complex and often uncertain. In addition, UVA output is measured with the detector's collecting surface placed at a distance from the source equivalent to the distance between the source and the patient's body surface during treatment; obvious variations in body contours and between patients introduces another source of error to UVA dosimetry.[56]

Not only may uncertain determinations lead to possible detrimental effects on the patient, but they make the comparison of different studies (to ascertain the risks and benefits of PUVA) both uncertain and difficult.[57] Recently, a new dosimeter specifically designed to meet the requirements of PUVA has been developed.[56]

CLINICAL USE

Clearing Phase

The patient stands in a whole-body irradiation cabinet lined with high-intensity UVA fluorescent bulbs. Units especially

designed for PUVA applications are now available.[58] Initially, treatments are given 2-3 times a week until the lesions begin to clear.[46] The frequency of treatments and the UVA dose may be increased gradually as a photoprotective tan develops.[45,59] In the 1979 Clinical Cooperative trial[18] however, a significant reduction in total UVA dose to clearing compared to the 1977 Cooperative trial[17] was achieved by using a "plateau" method in which no further increases in UVA dose were made as long as the lesions continued to clear.

Maintenance Phase

Neither PUVA nor any other therapy for psoriasis can provide a cure — only a remission. Maintenance treatments are initiated once 95% clearing has been achieved. Treatments are given once a week initially and the interval between treatments is increased or reduced as the symptoms allow.[17,18]

Precautions

Patients must wear opaque goggles over the eyes during irradiation as there is evidence from animal studies that UVA may cause cataracts.[60] Also, because the psoralen remains active for up to 6-12 hours after ingestion,[51,61] UV-filtering sunshades must be worn and sunscreens or clothing used to protect exposed skin surfaces if the patient is to be exposed to sunlight during this period.[46] Several comparative studies of commercially available eyewear have found Noir® 102 or 109 with side flaps (Recreational Innovation, Saline Michigan, U.S.A.) to be most effective at UVA reduction.[60,62] It is important to realize that UVA passes readily through glass[63] so that eye protection should be worn indoors for the few hours that the drug is present in active levels in the blood.

Mechanism of Action

Psoriasis is characterized by a marked increase in epidermal cell proliferation with an increased number of actively dividing cells, a shortened cell cycle, and a seven-fold decrease in the transit time from the stratum germinativum to the stratum corneum.[3,64,65] It is known that psoralen plus UVA inhibits epidermal DNA synthesis[66] and it is believed that this brings about the clearing of psoriatic lesions by preventing cell replication. Under the influence of UVA, the psoralen molecule forms covalent monofunctional photoadducts with thymine bases on the DNA strand and inter-strand cross-links between opposite pyrimidine base pairs.[61] In seeming contradiction to this mechanism, Hell *et al*[67] noted an increased proportion of epidermal cells in DNA synthesis during the early stage of PUVA in both involved and uninvolved skin. However, Bishop[68] demonstrated that increased DNA synthesis during PUVA may likely be a repair response to damage induced by the UVB component of the PUVA light source.

Although the inhibition of DNA synthesis is the generally accepted mechanism of PUVA action in psoriasis, Christophers *et al*[38] have pointed out that "the spectrum of disorders known to be sensitive to PUVA treatment raises challenging questions as to the mode of action of the therapy"; not all diseases responsive to PUVA are manifestations of epidermal cell proliferation.

Other possible subsidiary mechanisms of the action of PUVA have been investigated in a variety of disorders including psoriasis. Juhlin *et al*[69] found that UVA and the psoralen trioxsalen inhibited radially oriented fibrin crystallization in the blood of patients with psoriasis. As there is increased fibrin deposition in psoriatic skin, this finding suggests that fibrin inhibition may play a role in the action of PUVA. On the basis that prostaglandin (PG) levels are low in psoriatic skin, Heiligstädt *et al*[70] proposed that PUVA may act by increasing PG levels, but no evidence to support this hypothesis has been found.[70,71]

A decrease in neutrophils *in vivo* in psoriatics after they received PUVA therapy was reported by Dahl *et al*[72] who suggest the effect of PUVA may be to decrease the number of immunocompetent neutrophils present in the psoriatic lesion. Reese *et al*[73] suggested that PUVA action may be mediated by alteration of the abnormally high chemotaxis of mononuclearcytes characteristic of psoriatics but found no alteration of chemotaxis in patients who were cleared by PUVA therapy. However, Mizuno *et al*[74] reported that 8-MOP plus UVA greatly inhibit the activity of psoriatic leukotactic factor, a substance in psoriasis scales that has a chemotactic activity towards leukocytes responsible for producing Monro's abscesses, a feature of psoriasis.

In the treatment of vitiligo, a probable auto-immune disease, Roberts *et al*[75] have suggested that PUVA's action may be mediated through the generation of Ia-positive suppressor T-cells, based on evidence from PUVA irradiated mice. The melanocytes which repigment vitiliginous skin under the influence of PUVA are derived from a melanocyte reserve localized in the hair follicles.[45] Gilchrest[35] proposed that covalent photobinding of 8-MOP to DNA at the cellular level, and impaired T-cell function or survival at the tissue level are responsible for the therapeutic effect of PUVA in mycosis fungoides.

EFFICACY

The clinical results of 19 PUVA trials for psoriasis involving 2,508 patients are summarized in Table V. PUVA therapy has been demonstrated to be a consistently and highly efficacious treatment. The many trials done since 1974[1] typically report complete clearing of psoriatic lesions in 70-90% of patients, with close to 95% either completely clear or nearly completely clear.[1,6,17,18,49,52,76,79] In only a very few trials do 5% or more of those treated fail to respond to PUVA.[49,50,78,80] Longer courses of treatment or increased UVA doses are sometimes effective in clearing initially unresponsive patients.[67,78,80,81] These success rates equal or surpass those achieved by the most effective systemic drugs,[10] by tar,[87] or by anthralin.[78] In addition, PUVA is particularly efficacious in the treatment of generalized pustular psoriasis which is basically unaltered consistently by any other therapy except methotrexate.[6,19,77,86,88]

Special Areas

Because the action of PUVA depends on the penetration of the epidermis by UVA in order to photoactivate the psoralen, it is not useful in treating intertriginous areas, areas covered with dense hair, or psoriasis affecting the nails, during whole-body irradiation.[49] However, intertriginous or other localized areas can be treated separately with metal halide quartz lamps.[89] A very-high-intensity UV source has been developed which can deliver up to 250 times the normal therapeutic dose of UVA, ideal for treating radiation-scattering hirsute areas and radiation absorbing nails.[90] It is suggested that because UVA cannot penetrate to the synovium of joints,[91] PUVA is not effective in relieving

psoriatic arthopathy.[19,49] However, Perlman *et al*[92] reported a 50% improvement of non-spondylitic arthritis in psoriatics cleared by PUVA, although spondylitic arthritis was unresponsive.

TABLE V

Clinical Results of Puva Therapy for Psoriasis Concluding Initial Treatment Period

Study	n	in Rx	% CC	% MC	% IMP	%NR	% ADV
Parrish *et al*[1]	21	16	100	—	—	—	—
Swanbeck *et al*[82]	40	28.3	60	28	—	—	10
Wolff *et al*[76]	305	13.4	95	3	1.7	.3	—
Mizuno *et al*[83]	4	7.3	75	25	—	—	—
Weismann *et al*[83]	30	10.8	57	40	—	—	—
Melski *et al*[17]	1139	30	88	—	—	3	1
Lakshmipathi *et al*[50]	56	20	32	29	34	5	—
Hönigsman *et al*[6]	8	13.5	100	—	—	—	—
Nietsche[84]	26	22	65	27	8	—	—
Petrozzi *et al*[85]	24	23.4	58	12.5	21	4.2	4.2
Vella Briffa *et al*[78]	113	14.6	91	—	—	7	2
Wasserman *et al*[49]	51	37.5	78	10	6	6	—
Savin[79]	40	23	90	5	—	—	5
King *et al*[81]	53	19	57	26.4	—	1.9	5.7
Siddiqui *et al*[80]	107	32.2	52	40	—	8	—
Wagner *et al*[52]	21	25	79	19	10	—	—
Hell *et al*[67]	9	15	56	11	22	—	11
Coop Trial[18]	439	23.5	83	—	—	4.5	3.6
Murray *et al*[86]	22	26	55	23	18	4	—
Means for n =2508:		25.1	83	5.3	1.7	2.9	1.5

In Rx = number of treatments to complete clearing; CC = completely cleared; MC = marked clearance (50-95%); IMP = improved; NR = no response; ADV = adverse reaction to therapy. N.B.: all studies may not total to 100% as some patients discontinued therapy for personal reasons.

One treatment a week or one every two weeks are the most often required maintenance schedules,[1,17,49] although treatments once per month or at longer intervals were able to keep 35%,[18] 53%[50] and 77%[76] of patients in remission in three trials. Weismann *et al*[83] reported an average of five weeks remission with no maintenance treatments, and Petrozzi *et al*[85] reported four patients who remained clear for $2^1/_2$-3 months, and one for 10 months, without maintenance. PUVA remissions are not as long as those induced by tar (6 months to $1^1/_2$ years)[93] or by anthralin (7 months).[94] However, though the PUVA maintenance treatments are more frequent, they have greater patient acceptance than the messy tar treatments.[15,95] The clinical results of maintenance are summarized in Table VI

TABLE VI

Clinical Results of Puva Maintenance for Psoriasis

Study	N=	% of patients requiring treatments > 1/wk	1/wk	1/2wks	1/2wks	1/mo
Parrish *et al*[1]	21	—	100	—	—	—
Swanbeck *et al*[82]	17	47	53	—	—	—
Wolff *et al*[76]	135	—	11	12	—	77
Lakshmipathi *et al*[50]	34	—	47	—	—	53
Savin[79]	26	4	33	14	45	—
Wasserman *et al*[49]	30	—	67	23	—	10
Coop Trial[18]	271	—	28	18	18	35
Wagner *et al*[52]	20	55	35	10	—	—
Means for n=	552	3.6	31.2	14.1	11	39.7

PUVA For Diseases Other Than Psoriasis

A variety of other dermatological diseases have been treated successfully with PUVA. Christophers *et al*[38] attained a biopsy-confirmed clearance of urticaria pigmentosa. Dahl *et al*[41] reported that PUVA cleared erythrodermic seborrheic dermatitis in patients who were relapsing despite corticosteroid therapy. Atopic eczema has been treated successfully with PUVA[39,40] although twice the number of treatments required for clearing psoriasis were necessary and relapses were frequent whithout frequent maintenance. Alopecia areata has been effectively treated with topical 8-MOP and UVA after topical, intralesional and systemic corticosteroids had failed.[42] Topical 8-MOP,[19,43] oral 8-MOP,[19] and oral trioxsalen,[44] combined with UVA have been used in the repigmentation of vitiligo. PUVA has proven ineffective in the treatment of papulo pustular acne,[96]

Use In Potentially Fatal Diseases

One of the more promising aspects of PUVA is its efficacy in the treatment of the potentially fatal disease mycosis fungoides (MF). Histologically proven clearance of early stage MF[19,29-31,33,35] in patients unimproved by conventional therapies, and its use as an adjunctive therapy in more advanced stages[31,32] make PUVA a valuable treatment for this disease. Although success has been reported in the treatment of Sézary's syndrome with PUVA,[33,34] Fischer *et al*[97] reported a severe phototoxic reaction in one Sézary patient so treated. Four cases of parakeratosis variegata, an unusual clinical pattern of MF, have been successfully treated.[98,99] PUVA has proven to be very effective in controlling parapsoriasis en plaques, a pre-MF condition.[34] Histological clearance of lichen planus has also been demonstrated.[36,37]

ADVERSE EFFECTS

The most frequent adverse reactions to PUVA therapy — pruritus, erythema and nausea — are usually mild, temporary, and easily overcome. For pruritus, reducing exposure time or masking the affected regions will allow treatment to continue. If erythema is generalized, therapy is interrupted until it subsides. Nausea usually occurs only with doses of 8-MOP greater than 50 mg and can be overcome by ingesting the drug with a small meal or in half-doses $2^1/_2$ and 2 hours before irradiation.[53] Adverse reactions severe enough to warrant discontinuance of therapy affect only a very small percentage of PUVA patients (see Table V).

Other transient PUVA-induced reactions reported in the literature include bullous pemphigoid,[100,101] a clinically distinct acne — Acne aestivalis,[102,104] photoallergic dermatitis to 8-MOP,[105,107] hypertrichosis,[105,108,109] nevus-spilus-like eruptions and subungual hemorrhage,[107] and photoonycholysis.[110-112]

Although animal studies have shown that UV radiation can induce cataracts[113] and PUVA can induce eye tumors in mice,[114] there have been no reports of human eye damage attributable to PUVA. This may be due to the fact that the animal studies employ doses a hundred times greater than therapeutic doses,[60] and care is taken to guard the eyes of human patients during PUVA therapy.

Circulating Cell Cytotoxicity.

As 40-60% of UVA incident on the skin may reach the dermis[35,115] and bloodflow through psoriatic plaques is twice

that of normal skin,[116] there is a potential risk of cytotoxic effects on circulating cells in dermal papillae apices. Studies of chromosomal aberrations in lymphocytes of patients receiving PUVA have found no increased incidence of aberrations or sister chromatid exchanges (SCE) when the psoralen and UVA were administered *in vivo*.[82,116,117] The incidence of such aberrations in *in vitro* studies has been reported to be increased[82] or normal.[116] In studies of the effect of PUVA on lymphocyte function, no significant defect in lymphocyte blastogenesis or E-rosette formation has been found.[118-120] Although Morison *et al*[121] reported that a slight impairment of peripheral blood lymphocyte function as measured by lymphocyte response to photohemagglutinine (PHA) occurs in the first week of PUVA therapy, other studies[115,122] have shown no alteration of spontaneous or PHA-induced transformation. However, PUVA does have a lymphocytoxic effect *in vitro*.[123] Lymphocytes appear to play no role in PUVA-induced inflammation.[38] PUVA has been shown to reduce tritiated thymidine incorporation (a measure of DNA synthesis) of circulating leukocytes *in vivo*[124] and to increase the rate of SCE of leukocytes *in vitor*.[125]

Systemic Lupus Erythematosus (SLE)

One case of SLE has been reported in a patient receiving PUVA after she sunbathed against her doctor's advice.[126] No lupus erythematosus cell or serum fluorescent antinuclear antibody (ANA) tests were performed before treatment was initiated, so it is unclear what part PUVA may have played in the development of the disease. Millns *et al*[127] have noted the development of one case of an SLE-like syndrome after PUVA treatment. In another study,[128] 7 or 34 patients undergoing PUVA developed circulating ANA's which were not evident in pre-trial analyses. However, there were no other signs of collagenosis reflected by the serum protein pattern, urinary, or clinical findings as are usually found in a drug-induced SLE. Stern *et al*[129] reported that 1,023 patients participating in the 16 center cooperative trial[17] demonstrated no singificant increase of positive indirect immunofluorescent tests for serum ANA compared to pre-PUVA determinations. The mean follow-up for the group was 2.1 years.

Cutaneous Carcinoma

As the major mechanism of PUVA action involves the binding of psoralens to DNA, there is the theoretical possibility and a major cause for concern that PUVA may induce genetic alterations that will predispose to the development of cutaneous neoplasm. Despite the fact that psoralens and UV have been used for over 25 years in the treatment of vitiligo (in some patients for up to 10 years)[130] with no reported skin cancer attributable to the treatment,[63] there is the fear that the possible carcinogenic effects of PUVA may still become apparent in time.[21]

Animal studies offer no clear indication of the carcinogenicity of PUVA. Although PUVA has been reported to increase the incidence of tumors in mice when 8-MOP is applied topically or intraperitoneally,[114,131,133] other researchers report no increase when 8-MOP is given orally[133,135] even when a dose sufficient to produce severe burns and scarring was given.[136] Even a reduced incidence of carcinoma following oral 8-MOP and UVA has been demonstrated.[132] Scott *et al*[137] reviewed the PUVA animal literature, concluding that there is no evidence for increased risk of cancer to man, and pointed out that plants rich in psoralens — cloves, corriander, and fennel — are ingested daily by large numbers of people in India, Malaysia, Indonesia and Mexico with no apparent increased incidence of cancer, although their exposure to UVA (from sunlight) is far less than those receiving PUVA.

Cox *et al*[138] noted sites of epidermal dystrophy in half of 37 patients treated with PUVA, characterized by abnormal cells, similar to those seen in actinic keratosis and in some lesions resulting from light sensitivity, which may have been genetically altered and thus potentially dangerous. The authors admit that these sites may have been due to the 1-3% UVB output of their UVA source. This is in agreement with the findings of Pierard *et al*[139] that PUVA-induced damage differs from actinic damage. Omar *et al*[140] have also reported the presence of numerous cells with abnormal chromosome number and multinucleate cells in biopsies of PUVA-treated psoriatics. Other studies have shown no epidermal injury resulting from PUVA therapy.[21,59,141]

In a 2-year study of 1,373 PUVA patients, Stern *et al*[28] reported a total of 19 basal cell and 29 squamous cell carcinomas which arose in 30 patients. This incidence is 2.63 times that for an age, sex, and geographically matched population. Factors which greatly increased risk of carcinoma development were skin type (I and II), a history of ionizing radiation treatment, and a history of previous carcinoma, in order of increasing risk. There was no increased incidence of carcinomas in those patients with none of these risk factors.

Although this high incidence may be an artifact of the more thorough surveillance of these patients compared with the general population or discovery of pre-existing carcinomas once long-standing psoriasis was cleared,[28] several features of the reported tumors must be considered. The ratio of basal cell/squamous cell carcinomas for 18 tumors detected in the first year after PUVA was 2.6:1, comparable with the 3:1 ratio for overall incidence of these tumors in the USA. For the 30 tumors detected after more than one year of PUVA therapy, there was a statistically significant reversal of the ratio to 1:4. In addition, there was an excess of squamous cell carcinomas in areas not normally exposed to sunlight, while 75-90% of such tumors occur in sun-exposed areas in the population as a whole.[28] These anomalies may indicate that PUVA played a role in the reported carcinogenesis.

Similar cases of cutaneous carcinoma developing in non-sun-exposed areas of skin of patients receiving PUVA have been reported. Hofmann *et al*[142] reported two Bowenoid lesions, one case of Bowen's disease, and one keratoacanthoma in four PUVA-treated psoriatics. Tam *et al*[143] noted the development of multiple lesions of Bowen's disease and squamous cell carcinoma on the penis and pubic area of a psoriatic receiving PUVA. This patient had been treated previously with grenz rays, a risk factor identified by Stern *et al*.[28] Jesper[144] reported two cases of squamous cell carcinoma developing in 2 of 114 patients being treated with PUVA for MF. One patient had received prior X-ray treatment, a therapy previously noted to be associated with the development of squamous cell carcinoma in MF patients.[145]

Cutaneous carcinomas in sun-exposed PUVA-treated skin have also been reported. One patient treated with methoxsalen and sunlight for vitiligo developed multiple basal cell carcinomas; this patient had received arsenic treatment 8 years previously.[146] Roenigk[34] reported the appearance of a squamous cell carcinoma in a patient receiving PUVA for MF, whose only prior therapy was methoxsalen.

Is PUVA Worth the Risk in Psoriasis?

Nevertheless, Stern *et al*[147] point out that considering the limited morbidity of cutaneous carcinoma, and the substantial morbidity of severe psoriasis and the efficacy of PUVA as a treatment for it, candidates with severe psoriasis should be screened for the risk factors (skin type, history of ionizing radiation, history of previous carcinoma), fully informed of the possible risks, and if they consent, PUVA therapy should be implemented. However, the possibility that PUVA may produce internal carcinomas must be considered, particularly with the observed anomalies of distribution and type of cutaneous carcinoma associated with PUVA.[28] Recurrence of a rectal cancer in an MF patient,[37] and metastatic breast carcinoma, preleukemia[148] and acute myeloid leukemia[149] in psoriatics, all associated with PUVA therapy have been reported.

In no instance has any carcinoma been definitely attributable to PUVA therapy. However, these reports are cause for serious concern, and every effort is currently being made to mointor patient progress and dosage to minimize the total dose of UVA and psoralen required for clearing. Patients must be carefully examined throughout the course of the treatment and during maintenance for early signs of carcinoma development.

MODIFIED PUVA

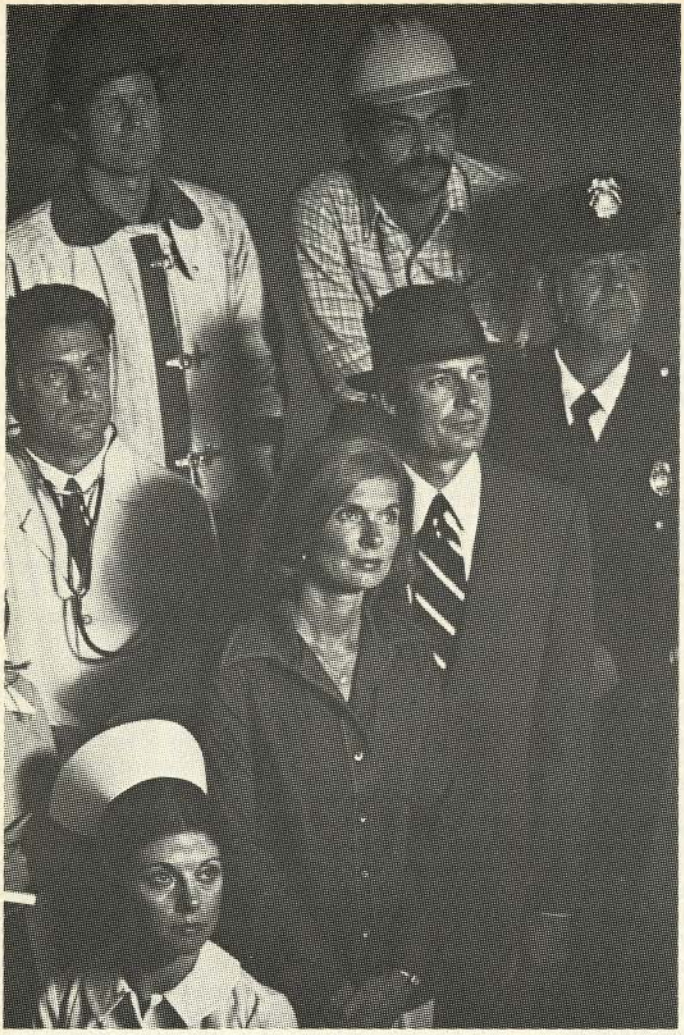
The oral-8-MOP-plus-UVA formula of PUVA has been modified with some success. Using filtered sunlight as an energy source, Robertson *et al*[150] reported complete clearance of 22 psoriatics. Other experimenters have combined PUVA with topical steroids[151,152] or a retinoic acid derivative,[153,154] or replaced oral 8-MOP with a trioxsalen bath,[48,155] and not only achieved dramatic reductions in total UV dose to clearing, but obtained good results in those patients who had proved unresponsive to conventional PUVA therapy. Hönigsmann *et al*[156] found that 5-methoxypsoralen (5-MOP) was as effective as 8-MOP in PUVA treatment of psoriasis, produced no erythema, blistering or pruritus in therapeutic doses, and even in high doses induced no nausea. *In vitro,* 5-MOP shows a greater affinity than 8-MOP for epidermis, resulting in a higher epidermal concentration than for an equal dose of 8-MOP.[157] UVA plus 3-carbethoxypsoralen has been found to produce results comparable to UVA plus 8-MOP, and has proved to be non-carcinogenic when applied topically or intraperitoneally and combined with UVA in mice[161] unlike 8-MOP.[114,131,133] DeBersaques[159] pointed out that despite the fact that PUVA therapy is indicated for psoriasis only when more than 30% of the body surface is involved,[46] PUVA maintenance is used to treat involvement of 5% or less, and suggests the use of anthralin, tar or corticosteroids to control these limited lesions and reduce PUVA exposure to the patient.

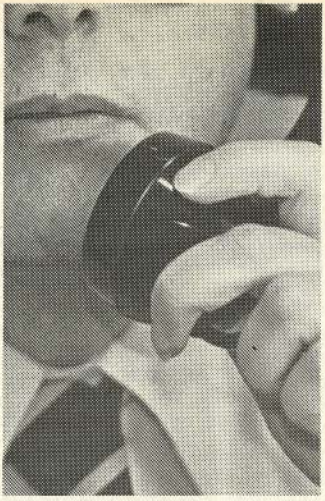
SUMMARY

There is no doubt that PUVA is a highly effective therapy with high patient acceptance, not only for psoriasis, but for a number of other disorders of the skin to which it has been applied; further applications may well be discovered. There is doubt, however about the safety of PUVA therapy, which has been associated with the development of cutaneous carcinoma. The development of improved equipment and techniques and the recent modifications involving adjunctive therapies are making PUVA safer by reducing the dose of psoralen and UVA to the necessary minimum for clearance.

PUVA therapy and equipment is complex and expensive and must be administered by highly trained and knowledgeable clinicians. It is not the treatment of choice for psoriasis. It is an experimental treatment, only for patients with severe or debilitating psoriasis for whom other treatments are ineffective or contraindicted. PUVA may well prove to be a remarkably safe treatment, but for the present, the watchword is caution. □

References available from author on request.





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Nephrogenic Diabetes Insipidus

NOVA SCOTIA AND LITERATURE

David B. Hogan,* M.D.,

Ottawa, Ontario.

Primary nephrogenic diabetes insipidus is a hereditary, sex-linked disorder of renal insensitivity to vasopressin. Aside from the polydipsia and polyuria, an interesting manifestation is a thirst for cold fluids. This rare disease is relatively more frequent in Nova Scotia. Historical data indicate that a female carrier of diabetes insipidus was among the 200 odd Ulster Scotsmen aboard the *Hopewell* which landed in Halifax on October 9, 1761. It has been suggested that the vast majority of primary diabetes insipidus in North America originates from these immigrants to Nova Scotia.[1]

The genetics of this disease are of particular interest. As a sex-linked disorder the full manifestations of the disease are, except in rare circumstances, found only in males. Carrier females, though, usually show a partial defect in urine concentrating ability.[1] With sex-linked (or x-linked) transmission, all the sons of affected males should be free from the defect and all the daughters heterozygous (or carriers). In carrier females half of male offsprings will be affected and half of female offspring will be carriers.

Not surprisingly, in the roughly 200 years of the existence of diabetes insipidus in Nova Scotia (especially in Colchester County), a detailed folk-lore concerning it has built up. Many of the facets of this folk-lore are summarized in a novel written by a Nova Scotian in the early years of this century.

In 1919, a novel, *Joan of Halfway* by Grace Dean Rogers (née McLeod) was published. Mrs. Rogers was born in 1865 at Westfield, N.S., and she was educated at Dalhousie and Acadia Universities, receiving her M.A. from Acadia in 1911. She had an obvious interest in Nova Scotia history and was the first female member of the N.S. Historical Society. Her other published works were predominantly about Acadian folk-lore. The Honourable Norman McLeod Rogers — the Minister of National Defence at the time of his death in 1940 — was her son. She died at the age of 93 in Toronto, Ontario.

Joan of Halfway was written for adolescent females. The story is how a young female orphan brings about the reconciliation of two warring branches of the Wisdom family and the reformation of her great uncle. Of particular interest is the presence of the "water drinker's curse" in the Wisdom family.

Some time in the past a male member of the family refused a drink to a wandering gypsy. The gypsy cursed that his "sons' sons and daughters' sons" would be afflicted with an insatiable thirst. While only males were fully affected, the female members of the family could show a tendency to water drinking. The curse could be ended by a "son's son." The Wisdom family was known for "too much marrying back and forth". Male family members were affected to a degree roughly equivalent to the "purity" of the Wisdom blood. The thirst was particularly for cold, spring water.

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As outlined, the understanding of the heredity is remarkably correct. The disease was known to run in families (particularly in-bred families) and to be a disorder predominantly of males. Females could show a partial defect, but not the full manifestations. The female family members could pass the disease to their sons. An affected male could, however, disrupt the chain of heredity. The passage from son to son is probably an expression of the inter-marrying. While the expressed pathogenesis seems ludicrous to us, it was a plausible as anything medicine had to offer until very recently.

Medicine only recognized the disorder and described the genetics in the late 1940's.[2,3,4] It is noteworthy that Nova Scotia folk-lore, as expressed by Mrs. Rogers, anticipated medical discovery by at least 50 years. □

Bibliography

1. **Bode H H and Crawford J D:** Nephrogenic Diabetes Insipidus in N.A. — The Hopewell Hypothesis. *New Engl. J. Med.* **280:** 750-753.
2. **Waring S G, Kajdi L and Tappan V:** Congenital Defect of Water Metabolism. *Am. J. Dis. Child.* **69:** 323, 1945.
3. **Williams R A and Henry C:** Nephrogenic Diabetes Insipidus: transmitted by females and appearing during infancy in males. *Ann. Int. Med.* **27:** 84-95, 1947.
5. **Dancis J, Birmingham J R and Leslie S H:** Congenital diabetes insipidus resistent to treatment with pitressin. *Am. J. Dis. Child.* **75:** 316-328, 1948.
6. **Rogers G D (McLeod):** *Joan of Halfway.* New York: G. A. Doran, 1919.

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An Appreciation

DR. J. CARSON MURRAY

Dr. J. Carson Murray, 72, of Springhill died March 30, 1980, at the Halifax Infirmary, after a lengthy illness.

Born in Tatamagouche, he was the son of Dr. Dan and Norna (Carson) Murray. He received his B.A. from Dalhousie University in 1928, and his M.D.C.M. in 1932. He underwent post-graduate training in surgery at Camp Hill Hospital, Halifax, and at St. Lukes' Hospital, Cleveland, Ohio. He then returned to Nova Scotia where he practised with his father in Tatamagouche for one year. In 1935, he came to Springhill where he spent the next forty-two years in the practice of General Surgery and Family Medicine.

For a number of years Dr. Murray was Chief of Staff at All Saints' Hospital, and served as Chairman of the Board of Directors. He was president of the Cumberland Branch of The Medical Society of Nova Scotia for three terms; for several years he was a member of the provincial executive of the Medical Society and the Provincial Medical Board of Nova Scotia. In October 1979, in recognition of his contribution to the practice of surgery, he was admitted to Senior Membership in the Surgical Section of The Medical Society of Nova Scotia. In November 1979, he received the award of Senior Membership in The Canadian Medical Association.

He was a life member of the St. John Ambulance Association and served as Divisional Surgeon of the Springhill St. John Ambulance Brigade for twenty-five years.

Dr. Murray was an avid woodsman; his many hobbies included music and sports such as swimming, boating, hunting, skiing, snow shoeing, and snowmobiling. During his university years he played clarinet in several of the orchestras on campus and was also on the Dalhousie football team.

Dr. Murray is survived by his wife Marion, the former Marion Burke, R.N., and by five sons and one daughter; Dr. David, St. John's, Newfoundland; Daniel, Dartmouth, N.S.; Dr. Harold, New Glasgow, N.S.; Stewart, Springhill, N.S.; Bruce, Toronto, Ontario; and Anne (Mrs. Bill Langstroth), Toronto, Ontario.

Dr. Murray gave selflessly of his energies and talents to the people of Cumberland County. His quiet and unassuming manner, coupled with a dry sense of humor, made his relationships with patients very special. He will be sorely missed. □

D.M. Rippey

Correspondence

To The Editor:

It has come to our attention that, when prescribing "Intal" for the first time, physicians do not always indicate that a Spinhaler must also be dispensed by the pharmacist, and pharmacists do not always check to see that the patient knows how to use this medication properly. Recently, a patient **swallowed** her "Intal" capsules several times a day for three weeks before complaining that she felt the medication had not improved her problems with asthma!

We would like to ask physicians to be sure the patient knows exactly why this drug is being prescribed, what equipment is necessary, and how to use this equipment properly.

Sincerely,

(Mrs.) Margaret Doane, R.N.,
Executive Director,
Asthma Society of Nova Scotia.

OBITUARIES

Dr. Hugh J. Brown (51) of Halifax, N.S. died August 8, 1980 at the Victoria General Hospital. Born in Sydney Mines, N.S. he graduated from Dalhousie Medical School in 1958. He was Medical Director at the Nova Scotia Institute of Technology, Halifax, from 1964 until his retirement in 1977.

Dr. William E. Fultz (78) of Glace Bay, N.S. died August 2, 1980 in the Glace Bay Community Hospital. He was born in Halifax and received his Medical Degree from Dalhousie University in 1925, he went on to specialize in Opthalmology at the Massachusetts Eye and Ear Infirmary. He practised in Glace Bay until his retirement. We extend sincere sympathy to his wife and children.

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JAMES R. JONES, M.D.
Orthopedic Surgeon
1440 Swampside St.
Gottingen, N.S.
Phone 999-4230

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Safety closure YES ☐ NO ☐
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Signature .....

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