THE NOVA SCOTIA MEDICAL BULLETIN

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An Explanation

It has been pointed out that the reference to Dr. Jim Reid in the April Editorial may have been misunderstood by doctors who do not know him. This might particularly apply to medical newcomers and those outside the Province who might read the Bulletin.

For the great majority of Nova Scotia doctors the Editorial elaboration of Dr. Mathers' facetious remark requires no explanation. To those others (and they are few) we might explain that Dr. Reid is one of Nova Scotia's most distinguished physicians with an enviable record as doctor, teacher and writer. It is in this context, with its appeal to the sense of the absurd that Dr. Mathers and the writer of the editorial expressed themselves. Its justification lies in the fact that the point could only have been made by using a figure of Dr. Reid's stature and reputation.

W.E.P.

Meetings? Meetings!

The cover of the April Issue of the N. S. Medical Bulletin announced that, in 1967, the Summer Meeting of the Society will be at the Pines Hotel, Digby, July 1 (Saturday) to 4 (Tuesday) inclusive; and that the 114th Annual Meeting and the 3rd Meeting of Council will be at the Hotel Nova Scotian on November 25 (Friday) and November 26 (Saturday) preceded by the Clinical Programme (the Dalhousie Refresher Course) November 20 (Monday) to 23 (Thursday) inclusive. Questions are being asked as to why there should be two meetings each year.

Over the last ten years there has been almost continuous study of the organization of the Society. Committee reports have been discussed by the Executive, and subsequent recommendations approved by the Annual Meetings. The result has been two series of amendments to the By-Laws, the first being approved by Governor in Council in 1962 when Sections within the Society and Affiliated Societies were authorized. In 1964, an amendment to the original constitution (1861) and a "Council" were approved. Chapter IX "Council", Article I reads:

> "The Council shall be the governing body of the Society with its action subject to the final approval of the Society and its Annual Meeting. It shall report to the membership of the Society and, as warranted, through the pages of The Nova Scotia Medical Bulletin."

The Council met for the first time in November 1965. The composition of Council is members in good standing of the Society representing 14 classifications. There is geographical representation as well as representation of all facets and interests in the broad fields of medical interests. The total membership on Council is approximately 130.

The first meeting of Council (November 1965) was successful. It had not been an easy achievement, but many who had opposed the concept, willingly conceded improvement over previous annual meetings and the inherent value in developing, through formal debate, policies which would be followed between these meetings. A very important action was the creation of the Physicians' Services Insurance Committee, which was authorized to discuss with any responsible government bodies the subject of Medical Services Insurance.

The second meeting of Council (November 1966) and the 113th Annual Meeting served to emphasize the justification of the amended By-Laws. Council, at that meeting, directed that meetings of Council and Annual Meetings take place in Halifax and that the Annual Dalhousie Refresher Course continue to be the clinical programme for the Annual Meeting. The Meeting of Council and the Annual Meeting of the Society will therefore be in the fall of each year, probably in November, in Halifax.

In the evolution of organization it became apparent that the tradition of annual meetings at summer resorts warranted examination before abandoning the principle. It was recognized that such meetings, if continued, should take place late in June or early July so as not to conflict with C.M.A. General Council, on which Nova Scotia has 10 representatives. Summer Meetings would also permit meetings of the Sections, of the Presidents and Secretaries of the Branch Societies and a meeting of the Executive Committee of the Society and finally, as the dates would probably be after school closed, it would create what Nova Scotian physicians particularly desire, an opportunity to bring the family along. The first Summer Meeting in 1966 at the Pines, Digby, was not only enjoyed by some 300 physicians, wives and family members, but resulted in productive business sessions and in a broad sense, can be regarded as a "curtain raiser" for the Meeting of Council and the Annual Meeting in November.

Let us not kid ourselves! With Medicare in the offing for July 1968 there is much yet to be done in creating for Nova Scotia a plan which will assure for the public quality medical care and for the profession those safeguards which will assure freedom of practice and the responsibilities associated with it, and a second meeting will assist in attaining this objective. □

C.J.W.B.

ERRATA

N. S. Medical Bulletin Volume 46 Number 4 (April) 1967, Page 75, for "Report of the Medical Advisory Committee" read "Report of the Medical Advisory Commission."

FORTY YEARS AGO

From the Nova Scotia Medical *Bulletin*, May 1927

By Ways of Medicine

It is our own feeling that there is more sound knowledge in Kant's "Kritik" than in all the literature of modern psychology. Still this does not mean that we see nothing of value in it and that it has nothing to teach us. We freely acknowledge that it may be of the highest value to us, though we cannot but agree with Dr. Selbie when he says that in reading Freud one has to wade through much unimaginable filth, and that he is driven to think that Freud himself is the victim of a sex complex. It is altogether beyond the scope of a short article, and also beyond our power to enter into an elaborate discussion of the nature and claims of the new psychology.

We are told that is is a science, and takes its place alongside of chemistry and physics. This only introduces confusion and leads to popular error, as there is no word in the language about which there is so much loose thinking as the word "science". Even the real sciences, for example, as chemistry and physics, may present to the world a varying amount of alloy in the way of imperfect observation and unverified hypothesis, but accurate observation and other means can cure this. In psychology, however, as possibly in economics and sociology the subject matter is so indefinite and shifting that we are not able to correct the mistakes in the same way that we can in the case of the true sciences, and it is quite possible that false authority may be imparted to inexact studies and speculations by labelling them "scientific".

A survey of the space given to psychologic medicine in the British Annuals shows a decreasing amount from the years 1922 to 1926.

This is possibly significant and might indicate that the British profession is paying less and less attention to psycho-analysis.

This is our own view. However, a chance conversation with a "Houseman" has led us to believe that the sinister spirit of Freud is still hovering over our land. □

HEAR YE, HEAR YE

Just a line to let you know that now is the time for all physicians to come to the aid of the Physicians' Services Insurance Committee. During May or June you will be receiving an assessment for $10.00, authorized by the 1966 meeting of Council, to offset some of the cost of this Committee.

Please give this your immediate attention when received.

C. DONALD VAIR, M.D.
Hon. Treasurer.

Medical-Legal Inquiries

THE BREATHALYZER

Q: My question is concerned with the Breathalyzer. Is not the requirement that drivers in Nova Scotia submit their breath to analysis an infringement of their rights against self-incrimination?

A: It is not at present a requirement in Nova Scotia that drivers submit to breath analysis, though in Saskatchewan, New Brunswick, Alberta and British Columbia it is an offence against the Provincial Motor Vehicle Acts to refuse to do so. The legality of these Provincial Statutes has been questioned as they would appear to be in conflict with the provinces of *Sec. 224* of the *Criminal Code* of Canada with respect to intoxicated and impaired driving where it is stated:-[1]

> "No person is required to give a sample of blood, urine, breath or other bodily substance for chemical analysis for the purposes of this Section and evidence that a person refused to give such a sample or that such a sample was not taken is not admissable nor shall such a refusal. . .be the subject of comment by any person in the proceedings".

Notwithstanding this, the Saskatchewan Legislature passed an amendment to *The Vehicles Act of Saskatchewan* in 1957 empowering the Highway Traffic Board to suspend or revoke the driving licence of anyone suspected of driving impairment who ". . .refused to comply with the request of a police officer. . . that he submit to the taking of a sample of his breath".[2]

This Section was held constitutional by the Court of Appeal for Saskatchewan[3] and was further appealed to the Supreme Court.

The majority of the Supreme Court Justices[4] upheld the constitutional nature of the Saskatchewan *Vehicles Act* as legislating in a field not covered by the Criminal Code, namely the holding of a provincial driving licence and the use of the provincial highways. Mr. Justice Taschereau, Messrs. Justice Rand, Fauteux, Abbott and Judson assenting, held that:-

(a) by the very words "for the purposes of this Section", Parliament indicated its intention not to trench the right of a province to create, for provincial purposes, a legal obligation to give a sample;

(b) the words "for the purposes of this Section", imply that for purposes other than the specific section of the *Criminal Code* referred to, a person might be required to give a sample;

(c) **Sec. 92 (4)** of *The Vehicles Act Sask.*) did not relate to the *Criminal* Code but to the administration and control of highways in the province for the protection of the travelling public.

(d) **Sec. 92 (4)** did not create a legal obligation to give a sample. It left the licence-holder the faculty to comply with or ignore a request and not a requirement; non-compliance did not amount to a violation of the enactment. The suspected licence-holder was in a position similar to that of any other person who, being suspected of a physical or mental affliction was requested to take an examination of fitness to drive.

On the other hand the Minority Report assented to by Messrs. Justice Locke, Cartwright and Martland, held that there was direct conflict between the provisions of the *Criminal Code* and the Provincial Statutes and that the provincial section was therefore **ultra vires,** as it was invading a field fully occupied by valid legislation of Parliament.

As the result of the majority report however the matter appears closed and the provinces of New Brunswick, British Columbia and Alberta introduced similar Breathalyzer legislation. The "average man" cannot be blamed if he is disturbed by the split nature of the decision particularly in view of the fact that all the Supreme Court Judges were in agreement that although the provisions of **Sec. 224 (4)** of the *Criminal Code* protect a person against providing a sample if he does not wish to do so, samples obtained under Provincial Statutes would be admissable under **Sec. 224** in prosecutions concerning violations of the Criminal Code.

The question of self incrimination however does not arise as it is entirely concerned with incriminating statements and not with incrimination conditions of the body, features, fingerprints, clothing or behaviour of the accused.[5]

I.D.M. □

References

1. C.C.C. **Sec. 224 (4).**
2. **Sec. 92** The Vehicles Act, 1957 (Sask.) C. 93.
3. (1958), 12 D.L.R. (2d) 470, 27 **C.R.** 369.
4. (1958) **S.C.R.** 608, 609
5. (1955) **S.C.R.** 593, *Atty. Gen. Quebec v Begin.*

Summer Meeting, The Pines, Digby, N. S.

July 1st, 2nd, 3rd, & 4th, 1967

You are invited to complete and return the Housing application form on this page.

Dr. G. McK. Saunders and his Committee Chairmen are developing the program which starts on Friday **evening** June 30. The detailed program will be outlined in the June Issue.

You can be assured of an interesting program which will include time for relaxation to enjoy the surroundings and pleasures associated with The Pines at Digby.

HOUSING APPLICATION FORM
The Medical Society of Nova Scotia
The Pines Hotel, Digby, N. S.
July 1, 2, 3. 4, 1967

Executive Secretary
The Medical Society of Nova Scotia
Dalhousie Research Centre
Halifax, N. S.

Please have reserved for me the following: -

Please check
IN HOTEL

1. ( ) Double room with bath - twin beds - including meals $17.00 per person per day. (accommodates 2 persons)

2. ( )*Single occupancy $20.00 per person per day. If attending alone please indicate with whom you wish to share accommodation.

IN COTTAGE

3. ( )Cottage $5.00 per day with sitting-room and two twin bedded bedrooms - including meals $17.00 per person per day. (accommodates 4 persons)

4. ( )Cottage $5.00 per day with sitting-room and three twin bedded bedrooms - including meals $17.00 per person per day. (accommodates 6 persons)

5. ( )CHILDREN under 14: Rate $9.50 per day per child. Please give ages of children accompanying you.

	Day	Date	Time
Date for arrival		AM	PM
Date for departure			

Name of persons who will occupy above accommodations:

NAME (please print) ADDRESS

.....

.....

.....

*In view of the attendance expected, single occupancy of rooms cannot be guaranteed. If coming alone and you are willing to share a room in the hotel, please check here.....

N.B.—Space will definitely be available at "The Pines" for applications received up to June 10, 1967 Accommodations at the Pines *or* a motel can be provided for applications received after June 10.

The Epidemiological Approach to Cancer Research
Smoking and Lung Cancer

P. C. Gordon, MD, DPH, CRCP(C)*
Halifax, N. S.

One of the objectives of cancer research is to identify individual attributes or environmental agents of etiologic importance. The epidemiological method in cancer research has an important role in this regard for, by studying the distribution of specific forms of cancer in a population and identifying the various factors that seem to influence this distribution, hypotheses may be developed concerning etiologic factors. Further, an etiologic hypotheses based on laboratory or clinical observation can be tested to determine if it is consistent with the distribution of the disease in human populations. From studies of this nature data are provided for the derivation of statistical associations between a disease and various characteristics of the population. From the pattern of associations derived, biological inferences may be drawn.

In general, two types of epidemiological studies are used to determine these statistical associations. First, studies of the distribution of the disease in the general population based on morbidity and mortality data and second, studies based on individual case histories which may be either of a retrospective or prospective nature.

These epidemiological studies deal with naturally occurring phenomena, in the sense that the investigator has no direct control over the factors that may influence the associations he observes. The problem is in deciding whether an associated characteristic such as cigarette smoking is related to the disease, lung cancer, as a direct, underlying cause or whether it is only indirectly related to the disease through some other factor or factors which are the real underlying causes. Obviously, a properly designed experiment is a more certain way of establishing the etiologic importance of the association but this is rarely possible in human populations. Thus we are faced with resolving the problem by other methods.

Recognizing that most, if not all, diseases have a multiple causation, for practical purposes, a factor may be defined as a cause of a disease if the incidence of the disease is diminished when exposure to this factor is likewise diminished. Lacking human experimental data, one must weigh all the available evidence and decide whether it is coherent and sufficiently convincing to place a cause and effect interpretation on the association and thereby begin positive preventive measures by removing, or at least lessening, exposure to the factor. Based on the concepts described by Lillienfeld[1] and Hill[2], and using smoking and lung cancer as examples, we shall review briefly some of the methods used to evaluate whether an observed association is indirect or direct and casual.

The Strength of the Association - Prospective studies in smokers have demonstrated that the death rate from lung cancer is nine to ten times the rate in non-smokers and the rate in heavy smokers is twenty to thirty times as great[3]. On the other hand, the death rate from coronary thrombosis in smokers is only twice as great as in non-smokers and one might attribute this latter association to some other underlying factor which is itself intimately associated with smoking, such as stress, diet or lack of exercise, smoking only being indirectly associated with the disease. However, it is much more difficult to explain a ten fold excess in lung cancer in smokers on the basis that some other underlying environmental agent is the real cause for any such agent must be so intimately related to smoking that it should be readily apparent, and in spite of much diligent investigation, no such agent has been found. Air pollution can account for only a small fraction of lung cancer for in studies where its effects have been controlled, smokers still have a far greater risk than non-smokers. Thus, in this case, the very strength of the association is good supportive evidence for a causal hypothesis.

The Consistency of the Association - Has the observed association been consistently shown by different persons, in different places, circumstances and times? Using a wide variety of individual techniques there have been 29 retrospective and seven prospective studies by various investigators in several countries and all have consistently shown a strong association between smoking and lung cancer.[3] It is most unlikely, therefore, that the association is due to some constant error or fallacy common to every study.

A further consistency is the fact that in the present generation, at least, the sex differential in smoking is in the same direction as the sex difference in lung cancer morbidity and mortality. On the other hand, the socio-economic differential for lung cancer and smoking has shown some inconsistencies.

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Lung cancer mortality is inversely related to socio-economic status but the frequency of smoking has not been found to be similarly distributed.

The distribution of the smoking habit in special population groups is consistent with the distribution of lung cancer mortality in these same populations. For example, in Israel, Jews originating in Europe smoke more and also have a higher mortality rate from lung cancer than Jews of Asian or African descent. Again, the Seventh Day Adventists in California who neither smoke nor drink have a lung cancer mortality 70% less than that of the rest of the California population.[4]

The Specificity of the Association - The hypothesis that the association between smoking and lung cancer is a direct causal one, has been severely criticized on the basis of a lack of specificity.[5] The concept of specificity implies that if a suspected etiologic factor is not restricted to one form of cancer but is found to be associated with other diseases, both neoplastic and non-neoplastic, the relationship with the particular form of cancer under study is less likely to be a direct one.

There are positive associations between smoking and twenty three causes of death with mortality ratios, of smokers to non-smokers, ranging from 10.8 for lung cancer to 1.1 for nephritis.[3] However, in evaluating the significance of these associations it is observed that many of them are very weak and, further, those diseases showing the strongest associations are all in areas of the body exposed to cigarette smoke and its products, namely, cancers of the lung, larynx and oesophagus and bronchitis and emphysema.

It is also apparent that if one is dealing with an impure substance, like cigarette smoke, the production of a number of diseases by the substance does not really contradict a causal hypothesis for any one of the diseases. Cigarette smoke may represent the vehicle transmitting a number of chemical agents each causally related to specific diseases. On the other hand, even if one deals with a single pure substance a variety of diseases may result from exposure to the agent. For example, mice exposed to X-rays develop a whole range of diseases both neoplastic and non-neoplastic involving many organs.[6] Similarly, humans unduly exposed to X-ray exhibit a nonspecific life-shortening effect.[7]

The Temporal Relationship of the Association - Particularly relevant to diseases of slow development is the question of whether a particular characteristic, suspected to be of etiologic importance precedes the onset of the disease or whether the course of the disease itself results in altered physical, emotional or social function leading to the development of the particular characteristic under study. This question of which is the cart and which is the horse freqently arises in studies of a retrospective nature. For example, studied retrospectively, certain social and personality characteristics have been shown to be associated with advanced coronary heart disease, but it is not at all clear that these characteristics preceded the development of coronary heart disease. Long term prospective studies are most helpful in clarifying this relationship and through studies of this type the temporal relationship between smoking and lung cancer is apparently quite clear.

The Biological Gradient or Dose Response Relationship - If one finds that the risk of developing the disease is linearly related to the degree of exposure to the agent then one's confidence in the causal hypothesis is certainly enhanced. In the case of cigarette smoking it has been repeatedly shown that the death rate from lung cancer rises linearly with the number of cigarettes smoked daily and further, that the risk decreases when smoking is stopped.[8]

The Biological Plausability of the Association - It is surely helpful if the causation we suspect is biologically plausable, remembering, of course, that what is biological plausable depends upon the biological knowledge of the day. Supporting the causal hypothesis for smoking and lung cancer is the fact that nine polycyclic hydrocarbons, plus arsenic, have been isolated from cigarette smoke which are carcinogenic for the skin of laboratory animals.[3,9] There is also the evidence of Auerbach[10] showing a histological change in the bronchial epithelium considered to be pre-cancerous which is more frequently found in smokers than non-smokers, the extent of which is dependent on the amount smoked.

Will another hypothesis adequately explain the association and what evidence do we have to support it? - On the whole the evidence considered so far seems coherent and tends to support a direct, or cause and effect, hypothesis for the association between smoking and lung cancer. However, as with any other scientific investigation one cannot accept an hypothesis simply because selected available data fit the hypothesis one has in mind. One must exclude other hypotheses that are also consistent with the data.

In a direct attempt to test the hypothesis that smoking is only indirectly associated with lung cancer, individuals who smoke have been compared with those who don't smoke with respect to many characteristics and no other common environmental agent of universal importance as a possible underlying etiologic agent has been found.

Sir Ronald Fisher,[11] in 1957, however, offered the hypothesis that cigarette smoking and lung cancer are indirectly associated, not through some other common environmental agent, but through the common factor of individual genotype. In other words, certain individuals are genetically predisposed both to smoke and to develop lung cancer. The genetic hypothesis is thus a major alternative to the smoking-causes cancer hypothesis and there is some evidence that gives plausability to it.

First, there is some evidence that smokers and non-smokers are morphologically different[12] and psychologically different.[13]

Second, there is some evidence that identical twins are more alike in their smoking habits than non-identical twins.[13]

Third, there is historical evidence that males are more predisposed to lung cancer than females. Lung cancer has been recognized since the early 1800's and many reports during the 19th century made it clear that the disease was recognized much more frequently in males.[15] Thus the male predominance for lung cancer apparently existed when smoking was a comparative rarity. Also, even though women have been smoking increasingly over the past 40 years, the wide disparity between the male and female rates remains.

Fourth, there is evidence of familial aggregation both for lung cancer and cigarette smoking. George Tokuhata[16] compared the lung cancer incidence and smoking habits in the families of lung cancer cases and in families of matched controls without lung cancer.

His findings are summarized as follows:

1. The relatives of lung cancer cases had an excess risk of lung cancer *with* or *without* the presence of smoking. No such excess risk was found among the spouses of the cases.
2. Men and women were equally likely to develop lung cancer if they were non-smokers, but men were more likely to develop lung cancer than women if they smoked.
3. Relatives of the cases were more likely to be cigarette smokers than relatives of controls. Again, no such difference was found among the spouses.
4. The degree of association between lung cancer and the familial factor was nearly as strong as that between lung cancer and smoking.
5. There is a synergistic interaction between the familial and smoking factors.

These results strongly suggest, therefore, that *both* the familial and smoking factors are directly associated with lung cancer and that each carries with it an increased risk. When both factors are present in the individual he has an even greater risk of developing lung cancer and this synergistic effect is more pronounced in men than women. If the familial factor represents a genetic component rather than a common environment, and this is supported by the fact that the spouses of the cases did not exhibit an increased risk of lung cancer, then the genetic hypothesis is compatable with, rather than alternative to, the smoking-causes lung cancer hypothesis. Thus, in spite of the fact that there may be a genetic component in the etiology of lung cancer, the evidence strongly suggests that smoking is at least one of the major etiological factors and the only major one we have any hope of correcting. □

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ADVERTISER'S INDEX

Treatment of Pulmonary Metastases From Carcinoma of the Breast*

GORDON W. BETHUNE, MD, CM, FRCS(C)
Halifax, N. S.

This paper is a review of patients with carcinoma of the breast who developed pulmonary metastases. Based on 792 patients seen in The Nova Scotia Tumour Clinic and in The Victoria General Hospital, Halifax, 152 of whom developed such metastases, the study was prompted by the frequency of, and the difficulty in controlling, this complication, particularly in patients with recurrent pleural effusion. The purpose of this presentation is to emphasize certain aspects of the disease itself, and to indicate some points in the diagnosis and treatment of this distressing complication.

Symptomatology and Diagnosis

Various interesting features came to light during this study. Because of the importance of the diagnosis of this type of metastatic disease, the major symptoms referable to the chest were reviewed (Table I). This Table refers to the patients operated upon. Some patients had more than one symptom.

TABLE I

SYMPTOMS OF 116 PATIENTS WITH PULMONARY METASTASES

None	68	(48.2%)
Shortness of breath	29	(20.6%)
"'Flu"	13	(9.2%)
Cough	9	(6.4%)
"Pneumonia"	8	(5.8%)
Chest Pain	7	(4.9%)
Malaise	7	(4.9%)

Thus, about half of the patients had vague symptoms pointing to pulmonary involvement *when the significance of their complaints was realized.* Most of them, if asked, admitted to shortness of breath, of having had an attack of " 'flu", pneumonia, or sime similar illness. It would appear that when one of these patients complains of a cough or a cold that "hangs on", the possibility of pulmonary metastases should be considered, and ruled out, before a more favourable diagnosis be accepted.

In the other half of the group *there were no symptoms at all* to suggest intrathoracic involvement. Pulmonary metastases were found in these patients only by routine chest X-ray. It would therefore seem advisable that all these patients have routine metastatic series, including chest X-ray, annually. More acceptable would be an even more frequent examination, though this would not seem feasible at present.

One interesting finding was that the incidence of pulmonary involvement was greatest in the age-group in which primary breast carcinoma is most common, thus correcting an erroneous clinical impression that intrathoracic spread was commoner in the younger patients.

Influence of surgery and irradiation upon metastatic spread

SURGERY: The suggestion is frequently made that surgical manipulation of a tumour tends to increase the chance of spread, due to passage of tumour emboli through lymphatic vessels and veins opened during surgery. The incidence of pulmonary spread in patients who underwent surgery and in those who did not is given in Table II.

TABLE II

THE INFLUENCE OF SURGERY ON THE INCIDENCE OF PULMONARY METASTASES

Treatment		Patients developing pulmonary metastases	
		No.	Percentage
Surgery	676	116	16.2
Other	116	36	31.0

It should be noted that, in the non-surgical group, decision against operation was influenced by the very finding of pulmonary metastases at the first visit. Nevertheless, it would appear that operation in itself does not increase the risk of intrathoracic spread.

IRRADIATION:

Comparing the incidence of pulmonary metastases developing in those patients who had surgery and radiation with those patients who had surgery and no radiation, shows that radiation did not affect greatly the incidence of pulmonary metastases. (Table III)

TABLE III

EFFECT OF TREATMENT ON INCIDENCE OF PULMONARY METASTASES

Treatment	Patients developing metastases	
	No.	Percentage
Surgery & Irradiation, 502	92	18.3
Surgery only 174	24	13.8

An additional and interesting finding in this review was that the pulmonary metastatic disease became evident at times varying from seven months to as long as ten years following the primary operative treatment.

*From the Department of Surgery, Dalhousie University, and The Victoria General Hospital, Halifax, and The Nova Scotia Tumour Clinic.

Management of the Patient with pulmonary metastases

Pulmonary metastatic disease is one of the commonest manifestations of secondary spread from breast carcinoma; it accounts for about one-quarter of all metastatic disease. As in any medical condition, our aim is to help the patient, and in this instance we can usually give some form of palliative therapy. There is no doubt that the lives of these patients may be prolonged considerably if they are treated properly, so that they may live in complete comfort and apparent health. For this reason early diagnosis is worthwhile and will influence treatment.

With regard to specific treatment, the patients fall into three groups:

i. Those with parenchymal lesions only;
ii. Those with pleural effusions only;
iii. Those with both parenchymal lesions and pleural effusions.

Patients with Parenchymal Lesions

It is important to consider first the need for oophorectomy. In general, in the majority of patients who are premenopausal or within a few years of the menopause, oophorectomy is advisable. In older patients this operation is unnecessary. In those younger patients in whom the single finding is a parenchymal lesion, oophorectomy alone may control the disease: some of these patients have lived for a number of years without other therapy.

However, some additional treatment is usually required. The types of treatment used with the patients in this group are presented in Table IV, together with the results.

TABLE IV

Treatment of Patients with Parenchymal Lesions

Results:	Good	Fair	Poor
Cortisone	15	10	6
Nitrogen Mustard (intravenously)	1	0	1
Stilbesterol	0	1	3
Testosterone	4	5	7

"Good" – The lesion remains static or becomes smaller and the patient is apparently well.
"Fair" – The progress of the disease is slowed and the patient feels subjectively improved.

Pleural Effusion

When the secondary deposit was manifested by recurrent pleural effusions, without parenchymal involvement, the most successful treatment was aspiration of the effusion followed immediately by an intrapleural injection of nitrogen mustard. The pleural cavity was aspirated as completely as possible, and through the same needle, usually one half to the total calculated dose of nitrogen mustard was injected. At times there was a reactive effusion within the next two or three days that required re-aspiration, but frequently there was no recurrence of the effusion for many months. Table V.

Although it is not noted here, an additional method of treatment that has been used successfully has been the aspiration of the pleural effusion and the intrapleural injection of a radio-active colloidal radio-isotope, usually gold. This is done in patients who continue to develop effusions after an attempt or trial of nitrogen mustard has been carried out.

TABLE V

Treatment of Patients with Effusion Only

Results:	Good	Fair	Poor
Cortisone	2	1	1
Aspiration and Nitrogen Mustard	10	7	4
Stilbesterol	0	0	11
Testosterone	0	1	2
Nitrogen Mustard (i.v.)	1	3	5

Parenchymal Lesions with Effusion

In the third group of patients, those unfortunate women who have both parenchymal lesions and pleural effusions, no form of treatment was of particular value. While the numbers are too small to allow any specific conclusions to be drawn, this group was the least responsive to treatment. (Table VI).

TABLE VI

Treatment of Patients with Parenchymal Lesions with Effusion

Results:	Good	Fair	Poor
Cortisone	3	3	2
Aspiration and Nitrogen Mustard	3	6	3
Stilbesterol	1	0	1
Testosterone	1	2	3
Nitrogen Mustard (i.v.)	1	2	4

Finally, and most interestingly, resection of the lobe of the lung affected by the metastatic disease was found to be curative in one instance. This may be considered if there is no evidence of any other metastasis in the body, and if the resection can be carried out completely. There is one patient in this category. A lobectomy was carried out approximately seven years ago for a proven metastatic deposit. This patient is still alive and well and shows no evidence of any other metastatic disease.

Conclusions and summary

Intrathoracic involvement from carcinoma of the breast is commonest in the age-group in which primary breast carcinoma is most common. In about half the patients there are no symptoms, the secondary being found on routine X-ray examination. In the others there are symptoms suggesting pulmonary involvement, such as a mild degree of shortness of breath and repeated attacks of "influenza".

When lesions are limited to the lung parenchyma, the best treatment is systemic cortisone, or in a few selected patients, resection of the involved part of the lung.

When there are repeated pleural effusions only, the best treatment is aspiration of the fluid and injection of nitrogen mustard.

When parenchymal lesions and pleural effusions occur together, treatment is not very successful, although combined cortisone and nitrogen mustard intrapleurally may give some relief.

Finally, although this is a very difficult complication to deal with, when treatment is successful there is a useful and satisfactory relief of symptoms. □

Carcinoma of the Lip*

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Carcinoma of the lip is the commonest tumour found about the oral cavity. The incidence of this tumour in Nova Scotia in the year 1964 was 2.2% of all malignancies. The incidence was 5.7 per 100,000 population. These figures are similar to those reported from other countries. This lesion occurs in a site where it should be readily recognized. However, patients are still being seen who have not sought medical advice early, thereby lessening their chance of cure. The delay is because this condition is usually painless. A very high percentage of cure should be obtained. Although one usually considers this lesion a well differentiated, slowly growing tumour, a small number are undifferentiated, rapidly growing and defy all present methods of treatment.

In order to determine the natural history of lip carcinoma in Nova Scotia and to assess methods of treatment, 204 patients who were diagnosed and treated during the years 1953 to 1959 inclusive in the Victoria General Hospital and followed in the Nova Scotia Tumour Clinic have been reviewed. The diagnosis was confirmed histologically in 190 of these patients. There were 202 males and 2 female patients. The carcinoma was of the lower lip in the two female patients. The average age was 66.2 years.

TABLE I

Age	No. Pts.
20–29	2
30–39	8
40–49	21
50–59	33
60–69	31
70–79	76
80–89	28
90–99	5
	204

In Table I, the incidence related to age is given. The largest number of patients (76) were in the eighth decade.

The carcinoma involved the lower lip in 94.1% of the patients. The upper lip was involved in 3.4% and the commissure in 2.4%. The extent of the lesion is considered to be of importance in determining the survival and treatment to be carried out.

TABLE II

Size of Lesion

1.5 cm or less	70.1%
1.6 - 3.0 cm.	21.1%
3.1 cm or greater	6.9%
Not recorded	1.9%

The extent of the lesion is recorded in Table II. The largest number were 1.5 cm. or less.

These tumours spread primarily by way of the lymphatics to the regional lymph nodes in the submental, submandibular and cervical areas. Lesions occurring in the mid-line may spread bilaterally. 2.9% of patients had involvement of the regional lymph nodes when first examined. Following treatment of the primary lesion, another 14.2% (29 patients) later developed metastatic involvement of the regional lymph nodes. Therefore a total of 17.1% of patients in this series developed metastatic tumour in the lymph nodes during some stage of their disease.

Cancer of Lower Lip

It has already been shown that the majority of lip carcinomas occur in the lower lip. Therefore in discussing the results of treatment, these are considered as a group. The accepted treatment of the primary lesion is either radiation therapy or surgical removal. In this series an opportunity has been afforded to make a comparison between these two forms of treatment. In the patients treated during the earlier years of the study, radiation therapy was primarily used. In the latter years this policy was changed to one favoring surgery because of a shorter treatment time, decreased morbidity, obtaining of a complete microscopic picture and a decrease in the complication of an atrophic lower lip. 192 patients were in this group and the various forms of treatment were as outlined in Table III.

TABLE III

Treatment Carcinoma Lower Lip

Surgery		
Wedge Resection	68	
Abbe-Estlander	9	
Total Lip Excision	5	
		82
Radiation		
Superficial	41	
Interstitial	68	
		109
Not Treated	1	1
Total Patients		192

Eighty-two patients were treated by surgical excision. For the smaller lesions a "V" or Shield excision was performed in 68. In nine patients having larger lesions, a full thickness rotation flap from the upper lip in a modified Abbe-Estlander

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procedure was performed. In 5 patients with very large lesions, it was necessary to carry out a Total Excision of the lower lip.

Radiation therapy was the primary form of treatment in 109 patients. Superficial radiation, usually under 250 kv was administered to forty-one patients, and interstitial radiation in the form of radium needles delivering approximately 6000 r was administered to sixty-eight patients. Superficial radiation was combined with the radium needles in three of the latter group.

One patient in this group did not receive treatment because of advanced carcinoma of the rectum.

In Table IV, is shown the number of patients according to the size of lesion and treatment carried out. In this way an attempt was made to compare those patients treated by surgery with those treated by radiation. It is seen that the number of those treated with lesions *less* than 1.5 cms. and those with lesions *greater* than 3.0 cms. are almost equal. In the middle group, those with a lesion between 1.6 cms. and 3.0 cms., eleven were treated by surgery and 30 by radiation. It is noted that in four of the radiated group, the size of the lesion was not recorded.

TABLE IV

CARCINOMA OF LOWER LIP

Size of Lesion

	0 – 1.5	1.5 – 3.0	3.1 +	Not Recorded
Surgery	64	11	7	
Radiation	69	30	6	4
Not Treated	1			
Total Patients:	192			

In considering treatment of the primary lesion, the first point is control of the disease locally. In Table V, the local recurrence rate related to treatment is given.

TABLE V

CARCINOMA OF LOWER LIP

TREATMENT OF PRIMARY	LOCAL RECURRENCE RATE
Surgery	4.9% (82 pts.)
Radiation	9.1% (109 pts.)
Superficial	12.2%
Interstitial	6.2%

Local recurrence of the carcinoma was found in 4.9% of those treated by surgery and 9.1% of those treated by radiation therapy. It was found that the largest number of recurrences occurred in those patients who had received superficial radiation therapy. These patients having an incidence of 12.2% compared to 6.2% in those treated with interstitial radiation.

The time of recurrence in those treated surgically was 6.4 months, with superficial radiation it was 20 months and with interstitial radium 14 months.

These figures indicate that either surgery or radiation results in effective control of the local disease. Superficial radiation therapy would not seem to be as effective in controlling the disease as either surgery or interstitial radiation.

Of the local recurrences following surgery, 5 of the 6 were successfully treated by subsequent radiation therapy. One patient was not treated because of the very extensive and rapid recurrence. Of the four recurrences following interstitial radiation, two were successfully treated by surgery and one by further radiation. Of those recurrences following superficial radiation, five were controlled by further surgery, and one, treated by radiation, continued to have extensive disease.

It would therefore appear that local recurrence of carcinoma of the lip may be controlled in four out of five patients by either further surgery or radiation therapy.

The second consideration in the treatment of lip carcinoma is that of tumour in the regional lymph nodes. Disease in these sites is treated surgically by radical neck dissection when the diseased lymph nodes can be removed completely. Radiation therapy is used for palliation when considering disease in this area. Regional lymph node metastases were present in 6 or 3.1% of patients with carcinoma of the lower lip when first examined. Another twenty-eight or 14.6% subsequently developed disease. Four of the twenty-eight patients had bilateral metastatic disease.

Before considering the results of treatment here, it is worthwhile reviewing the type of treatment used to control the primary disease and relate this to the subsequent development of metastatic disease.

TABLE VI

CARCINOMA OF LOWER LIP

TREATMENT PRIMARY LESION	REGIONAL RECURRENCE RATE
Surgery	13.4%
Radiation	15.6%
Superficial	7.3%
Interstitial	20.6%

In Table VI, the incidence of metastatic tumour in the regional lymph nodes is related to the type of treatment used to control the primary lip carcinoma. In those treated surgically, 13.4% developed metastatic disease in the regional lymph nodes and in those treated by some form of radiation therapy, 15.6% developed metastases. The incidence was 7.3% in those who had superficial radiation therapy and 20.6% in those whose who were treated by interstitial radiation. This is suggestive that interstitial radiation therapy may play some part in the subsequent development of regional lymph node metastases. In all, twenty-eight patients developed metastatic disease in the regional lymph nodes. Of these 39.3% survived five years.

In Table VII, the results of treatment in those patients who developed regional metastatic disease is given.

TABLE VII
REGIONAL METASTASES

	NO. PTS.	ALIVE AT 5 YRS.	
Radical Neck			
Unilateral	19	10	53.4%
Bilateral	3	1	33.3%
Suprahyoid Dissection	2	0	0%
Radiation	2	0	0%
No Treatment	2	0	0%
Total Patients	28	11	39.3%

In those patients where the recurrence was extensive and not considered resectable, either radiation therapy or no treatmet was carried out. This was the situation in four patients and all were dead within five years. In another two, a suprahyoid dissection was performed and both died of their disease within five years. As already mentioned, the curative procedure for regional metastatic disease is a radical neck dissection. This was unilateral in nineteen patients and bilateral in three patients. In the unilateral group 53.4% were alive at five years, and in the bilateral group one was alive at five years.

These results show that 28 out of 186 patients required subsequent treatment of the regional lymphatic drainage area. If prophylactic neck dissection had been the policy, 158 procedures would have been done unnecessarily. Therefore, the policy should continue of following the patient regularly after treatment of the primary lesion and when lymph nodes became palpable, a biopsy is done. If positive for metastatic disease, a neck dissection is performed.

There were six patients in whom the regional lymph nodes were involved when the patient was first examined. Only one patient was alive at five years. Four died of their disease and another died of other causes.

Cancer Upper Lip and Commissure

In another group, of twelve patients, there were seven with carcinoma of the upper lip and five with carcinoma of the commissure. Of these twelve patients, eleven were treated with radiation therapy and three subsequently developed local recurrence. One patient developed regional lymph node metastases. The crude five-year survival of this small number of patients with carcinoma of the upper lip was 85.5% and the commissure 60%.

Survival Rate

In considering the survival rate of these 204 patients with lip carcinoma, it is to be pointed out that all patients were followed for at least five years or until the time of their death. It has been stated that crude survival rates for cancer of this site are almost meaningless and that net survival rates should be used because this factor assumes that the patients untraced or dead from other causes would have had the same experience regarding the lip cancer as the patients for whom the five-year outcome was known. In the present group, the net survival rate when calculated is 100%. However, with the crude five-year survival one can determine exactly what the survival is and then question the cause of death in those non-survivors at five years after diagnosis.

The crude five-year survival was 75% in all 204 patients. When one considers the other causes of death in the group of non-survivors, some interesting facts are revealed. First, 9.3% died of lip carcinoma within five years of diagnosis. Secondly, 2.5% died within a five year period of a second carcinoma elsewhere in the body. 12.7% died of other causes, these being chiefly related to the cardiovascular system. These figures therefore show that a patient can die of carcinoma of the lip and that it must always be considered a serious disease.

In this group another interesting finding has been that four developed a new primary carcinoma of the lip, an incidence of 2%. Also, there were twenty-three or 11.3% who developed a second carcinoma. Therefore, when one includes all subsequent carcinomas there was an overall incidence of 13.2% within five years. This is another reason for careful follow-up of patients.

Summary

In summary, 204 patients with carcinoma of the lip who were treated during the years 1953-1959 have been reviewed. The ratio of female to male was 1 to 102. The average age was 66.2 years. 2.9% of patients had involvement of the regional lymph nodes when first examined and 14.2% subsequently developed regional lymph nodes. In considering treatment of lip carcinoma, a comparison has been made between surgical and radiation forms of therapy for the primary lesion. Surgery was followed by a local recurrence rate of 4.9% and radiation therapy by 9.1%. Interstitial radiation was more effective than superficial radiation in controlling the primary disease. Recurrence of disease at the primary site was effectively controlled by further surgery or radiation in four out of five patients. In carcinoma of the lower lip, regional metastases developed in 13.4% of patients who had surgical excision and 15.6% of patients receiving radiation therapy. The incidence of regional metastases was higher (20.6%) in those receiving interstitial radiation. Radical neck dissection was the only effective way of treating regional metastatic disease, 53.4% of those patients having a unilateral neck dissection surviving five years. One of 3 patients requiring bilateral neck dissection surviving five years. Carcinoma of the upper lip and commissure were effectively controlled with either superficial radiation or interstitial radiation.

The crude five-year survival in 204 patients with carcinoma of the lip was 75%. It should be emphasized that 9.3% of patients dead at five years died of lip carcinoma. 2.5% died of a second carcinoma. □

Treatment of Multiple Myeloma*

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Multiple myeloma and its allied conditions, plasmacytoma, solitary myeloma and plasma cell leukemia, are malignant proliferations of plasma cells primarily of bone marrow. On occasion these proliferations occur in other sites such as the nasopharynx and thoracic cavity. The most characteristic feature of this tumor is its propensity to destroy bone. Bone pain was the presenting complaint in more than 70% of patients seen at the Victoria General Hospital. Bone destruction produces collapsed vertebrae, pathologic fractures of ribs and long bones and hypercalcemia. Collapsed vertebrae or tumor outgrowth from a vertebral body may cause pressure on the spinal cord producing paraplegia. Paraplegia may therefore complicate recognized myeloma at any time or be the presenting feature as it was in 3% of our patients. Anemia, leucopenia and thrombocytopenia are common and anemia has been the presenting problem in a significant number of our patients. The anemia is mostly due to failure of the bone marrow to produce adequate numbers of red blood cells.

The function of normal plasma cells seems to be primarily related to the immunological system and in particular these cells synthesize those serum globulins that function as antibodies (immunoglobulins). The family of antibodies or immunoglobulins has at present four well established members. The present terminology of the immunoglobulins is outlined in Table I. The malignant plasma cells in myeloma usually retain the ability to produce one type of immunoglobulin. Since the plasma cell growth is greater than normal, the immunoglobulin is produced in excess. In 80% of our patients with myeloma we found hyperglobulinemia due to an elevation of one of the immunoglobulins G or A. Characteristically if one of the immunoglobulins is elevated in myeloma the others are depressed to about 10% of their normal values. The production of a large amount of immunoglobulin in myeloma results in a narrow "spike" of protein in the electrophoretic strip. The malignant plasma cells probably produce one immunoglobulin only as it behaves as a homogeneous band on electrophoresis. For an example of the electrophoretic strip seen in myeloma see Figure I. The immunoglobulin molecule is made up of two identical polypeptide chains of molecular weight 50,000 (heavy chains) and two identical polypeptide chains of molecular weight 20,000 (light chains). When light chains are produced in excess, they are excreted into the urine where they are recognized as Bence Jones protein. If Bence Jones protein is excreted in the urine, it also results in a narrow band on urine protein electrophoresis.

To establish the diagnosis of myeloma one should obtain histological material, either marrow aspirate or tissue biopsy. In addition to the clinical features noted in the introduction, certain laboratory findings suggest that myeloma should be considered in the differential diagnosis. The electrophoretic pattern seen in Figure I is most frequently associated with myeloma. It may also be seen in macroglobulinemia, rarely with lymphoma, other cancers and perhaps with no pathological states on occasion.[1] Osteolytic bone lesions without bone reaction are also common in myeloma. However, demineralization is also frequent and even sclerosis can be seen.[2]

TABLE I
IMMUNOGLOBULINS (GAMMA GLOBULINS) IN MAN**

NAME	SYNONYM	NORMAL VALUES	COMMENT
Immunoglobulin G (Ig G)	Gamma G, γ G	700–1500 mgs%	One of Ig G, Ig A, or Ig D are elevated in myeloma. Increased levels of Ig G are found in 50% of myelomas, Ig A in 24%, Ig D in 3%, Bence Jones only in 21%.
Immunoglobulin A (Ig A)	Gamma A, γ A	50–250 mgs%	
Immunoglobulin D (Ig D)	Gamma D, γ D	3 mgs%	
Immunoglobulin M (Ig M)	Gamma M, γ M	60–170 mgs%	Ig M elevations without an elevation in the other immunoglobulins may be seen in Waldenstrom's macroglobulinemia.

**Hypergammaglobulinemia may be monoclonal in which a single immunoglobulin is present in excess and characteristically migrates as a "spike" by electrophoresis, or polyclonal when there is an elevation in several immunoglobulins which shows up as a broad elevation of gamma globulin on electrophoresis. In monoclonal hypergammaglobulinemia only one of Ig G, Ig A, Ig D or Ig M are elevated while in polyclonal hypergammaglobulinemia characteristically two or more of the immunoglobulins are elevated.
Hypogammaglobulinemia indicates a decrease in level of one of Ig G, Ig A, Ig M or Ig D. On occasion the deficiency in one of the immunoglobulins may not be obvious by electrophoresis since an elevation in one of the others may mask the deficiency. Immunoelectrophoresis and Immunodiffusion studies will reveal the true deficiency.

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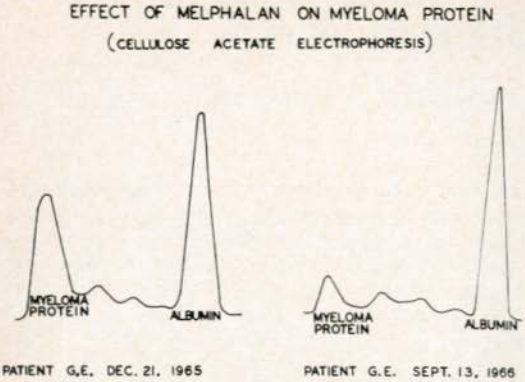


Fig. I. The patient's serum electrophoresis before treatment is shown on the left. The myeloma protein (an Ig G) was 3.6 gms% initially. A low molecular weight protein was present in the urine which migrated as a homogenous protein (Bence Jones). After 10 months treatment with Melphalan, 2 mgs. daily to 2 mgs. five days a week, the myeloma protein was reduced to 0.8 gms% shown on the right. IG A was 16% of normal and Ig M 9% of normal in this patient. (See also Figure 3A and 3B).

TREATMENT OF MYELOMA

Therapy directed to the destruction of the malignant proliferating plasma cells depends on the extent of the tumor. For solitary myeloma (plasmacytoma), radiotherapy is indicated since large doses can be administered to a small area. If, however, there is evidence of widespread disease (multiple myeloma), chemotherapy becomes the treatment of choice and radiotherapy is only used as an adjuvant to treat local tumor growths which are causing local effects.

Chemotherapy of Myeloma

Two analogues of nitrogen mustard are being used with some success to treat multiple myeloma, chlorambucil and melphalan. In our experience, melphalan has been the more satisfactory drug for initial treatment. In sixteen cases treated with this drug we have seen reduction in the serum myeloma protein (Figure I), healing of bone lesions (Figures 2, 3) and improvement in symptoms of bone pain. The number of patients who will benefit from melphalan is not clear as yet but from our experience probably about one-third will show significant improvement. The improvement takes place over many months and in our experience may continue into the second year of treatment. Melphalan and Chlorambucil have major toxic effects on the bone marrow and frequent evaluation of hemopoietic function is essential to control drug administration.

During the natural course of patients with myeloma a variety of symptoms and complications may occur each of which may require a specific therapeutic program. When a new symptom arises in a patient with myeloma, it is important to identify the cause since the treatment will depend on this. For example, nausea can reflect drug toxicity, hypercalcemia or renal disease due to infection or myeloma protein induced nephropathy. The therapy would of course depend on which of these was at fault. Certain recurring problems occur, however, and the therapy of these will be considered.

Bone Pain

This is the commonest and most distressing symptom patients experience. Even when not severe, its continual presence and aggravation by movement is so distressing that most patients become depressed. Because skull lesions, even when

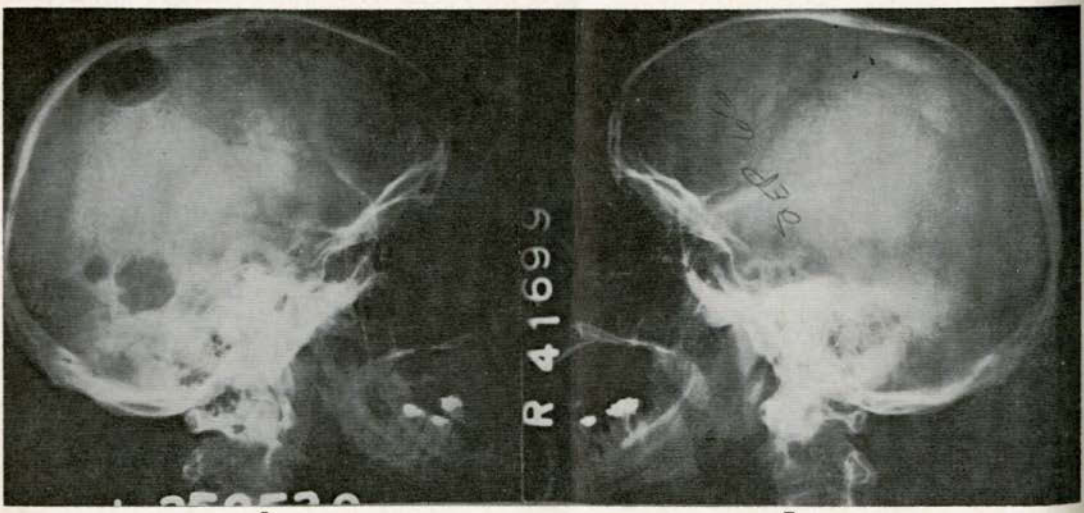


Fig. 2. Left: several large osteolytic defects are visable in the skull. After one year of Melphalan, 2 mgs. daily, the lesions have healed (right) and there is increased bone density in previously lytic areas. Lytic lesions in pelvis and scapula showed similar healing.

extensive, do not cause pain, we believe the rib and vertebral body pain is not due solely to tumor, but to associated fracture.[3] Conventional X-rays, however, may show only osteolytic lesions or demineralization. Unfortunately, bed rest may lead to further demineralization in an already osteoporotic spine so a judicious balance of activity and rest must be achieved. Support for the vertebral column by a brace is usually required. The brace must be carefully fitted and padded over bony prominences lest it causes more discomfort than it relieves. If a relatively localized area of discomfort is identified, radiotherapy may prove helpful. The tumorcidal effects of the chemotherapy may over a period of time allow bone healing and reduction in bone pain. In an attempt to improve the osteoporosis so often present, sodium fluoride has been used, although in our experience, melphalan alone is as likely to cause bone healing as melphalan with sodium fluoride. The usual analgesic agent we use is codeine, 30 mgs., and we can judge the progress of the bone pain by the amount of Codeine required to provide relief over a 24 hour period.

Paraplegia

This is a frequent complication in myeloma. Surgical decompression of the spinal cord must be carried out as soon as the first symptoms appear. Once complete paraplegia is established, there is likely to be little or no return of function so that early recognition is important. As soon as the patient complains of weakness in his legs, paresthesias or change in his gait, a prompt and complete neurological examination with a myelogram is usually indicated. If decompression can be performed early, the patient is usually able to resume activities with a fitted brace.

Hypercalcemia

Hypercalcemia may produce many symptoms including drowsiness, irritability, nausea, vomiting and polyuria. The hypercalcemia can usually be corrected by the use of steroids, hydration and chemotherapy.

Anemia

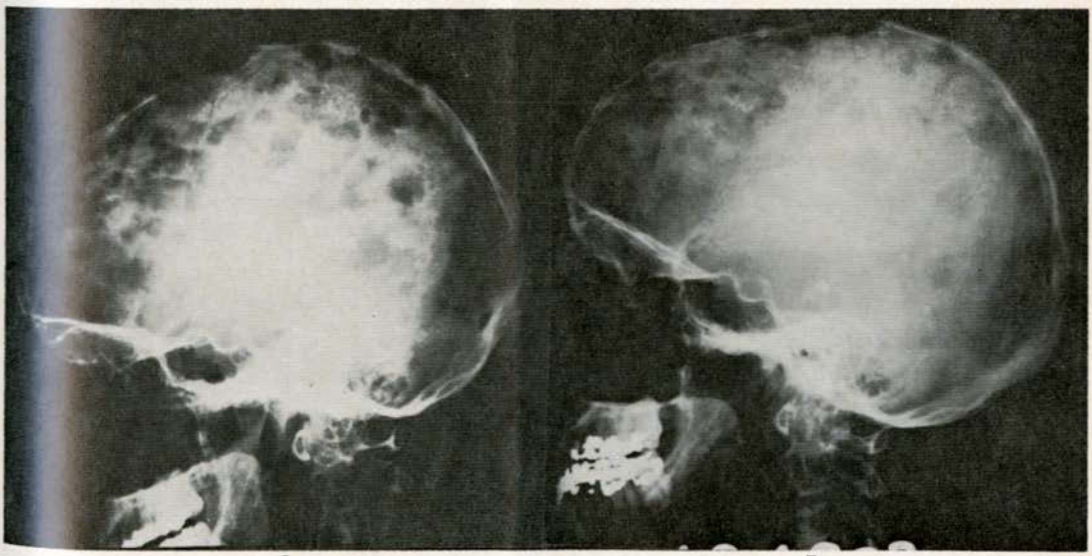
If the tumor responds to the chemotherapy there is usually a rise in hemoglobin, otherwise transfusions are required. We do not often use transfusions to combat mild anemia, however, since patients with a hemoglobin of 9 gms% or greater are often not greatly affected by their anemia.

Recurrent Infections

As discussed previously, patients with myeloma have decreased levels of normal immunoglobulins, and in addition leucopenia is common. The chemotherapeutic agents used to control the disease also suppress host defence mechanisms. Recurrent infections are therefore frequent. While we have never found prophylactic antibiotics to be of benefit, prompt initiation of antimicrobial therapy when fever occurs after appropriate specimens have been taken for culture is important. Characteristically septicemias, pulmonary and renal tract infections occur and unusual bacteria or fungi are not uncommon.

Pathological fractures

Pathological fractures are likely to occur at some time in most patients with myeloma. It is important therefore to outline a program which will help to prevent fractures in these patients. Huge shear forces are exerted on the bones by twisting movements and these and sudden movements should be avoided. Slippers and shoes should have



A B

Fig. 3. Left: numerous lytic lesions are visable throughout the skull. Ten months later (right) after melphalan, 2 mgs. daily to 2 mgs. five days a week, many of the lytic lesions have healed and many are healing.

rubber soles, loose floor mats should be removed, and care must be exercised on steps, curbs (stepping up and down), and getting into and out of bath tubs. Fortunately, in spite of the tumor tissue present, fractures may heal satisfactorily. The fractures seem to heal equally well whether local radiotherapy is given to the area or not although we have usually given a course of treatment. By the time a fractured femur occurs there is usually extensive bone destruction in the area. The immobilization required to get good union leads to muscle atrophy and there is, therefore, often difficulty in getting these patients walking again. Rib fractures heal well and we usually do not provide local support to the area.

Summary

Myeloma, a plasma cell malignancy, is a tumor primarily of bone and bone marrow associated with marked changes in the patient's immunological system. Treatment is directed to control of the tumor mass with radiotherapy or chemotherapy and to the treatment of symptoms and complications. Of these, bone pain, pathological fractures and recurrent infections are most susceptible to treatment. □

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BOOK REVIEW

The Medical Annual - 1966 Edited by Sir R. Bowdley Scott and R. Milnes Walker.
Published by John Wright & Sons, Bristol, 619 pages.

This book is published yearly and has contributions from many prominent British physicians. Each author provides several short concise articles on related subjects of current interest. They encompass all branches of medicine and medical specialties. Specific anatomical or physiological subjects are dealt with firstly from a medical and then from a surgical standpoint where this is applicable. For the first time, in this edition there is a section devoted to general practice.

Each author presents the meat of several current medical publications on a selected topic in easily digestible form. Tentative conclusions are reached about many difficult problems in the light of known facts, reasonable hypotheses, and especially the careful consideration of statistical analyses. Each article is followed by a list of references. It is not intended as a textbook which would give a comprehensive discussion of all aspects of each disease, but as a series of reference articles which could well be considered as addenda to be pinned at the end of the corresponding section in a standard textbook.

This book would be very useful for the general practitioner as an aid in keeping abreast of current medical developments, providing a maximum of information in a minimum of space. It is also a useful publication for specialists, since it points up areas of current interest in one's own specialty and provides valuable information about other fields.

J.M.MacS.

Cutaneous Moles and Melanomas*†

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Benign pigmented naevi and malignant melanomas are derived from pigment-producing cells of the basal layer of the skin. Moles are very common; the average person has ten to thirty.[1] Malignant melanoma is uncommon but not rare; about thirteen new cases arise each year in Nova Scotia.

Most melanomas either arise from moles or are mistaken for moles. Unselective removal of all moles for prevention or early diagnosis of melanoma would be an absurdity since the proportion of unnecessary to useful excisions would be in the order of many thousand to one. Yet some moles should be removed because their location or clinical features make them suspect. A knowledge of the behaviour of malignant melanoma along with a suspicious frame of mind will aid us in selecting moles for excision.

The sex of the patient is of no help in making this decision as malignant melanoma occurs with about equal frequency in both sexes. The age of the patient is of some value since melanoma is predominantly a tumour of persons over 30 years, although young adults and children are not exempt. In a review of 135 patients with histologically proven malignant melanoma in Nova Scotia[2] we found the median age at time of diagnosis was about 50 years; the oldest patient was 88 and the youngest was 12. Five patients in our series were teen-agers, and younger children and infants have been reported, although rarely, with malignant and lethal melanomas.

The location of a mole may be very important. Certainly those on the palms, soles, and genitalia should be removed without question, for a pigmented lesion in these situations is very likely to be either a melanoma or a junctional naevus with malignant potential. A pigmented tumour which is situated where it is likely to be injured by usual activities or irritated by belts and straps should likewise be removed, if only to eliminate trauma as an explanation for the significant changes which are discussed below. A black area in a nail bed which increases under observation is not likely to be a haematoma and may be a subungual melanoma (Figure 1). Some moles will, of course, be removed for purely cosmetic reasons, but even so the method of removal should be one that pays deference to the possibility that the lesion may be malignant.

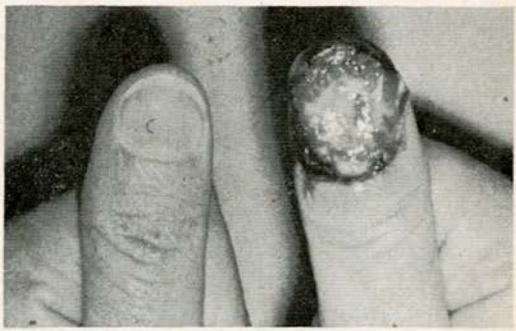

Fig. 1. Hutchinson's melanotic whitlow or subungual melanoma on the right thumb of a 37 year old woman. The history included trauma, appearance of black colour about the nail bed, and spontaneous loss of the nail.

The gross appearance of a mole is a useful guide to its malignant potential. The typical junctional naevus (figure 2), from which many melanomas arise, is smooth, flat, hairless, and looks like a spreading drop of brown or black paint. Junctional naevi are premalignant lesions, and while the likelihood of any single junctional naevus becoming malignant is not very great, they should be viewed with suspicion in adults. Unfortunately melanomas may also arise from junctional elements in warty and hair-bearing naevi, which are usually considered to be relatively safe. Once a melanoma starts in any naevus, the appearance may be altered, as is discussed below.

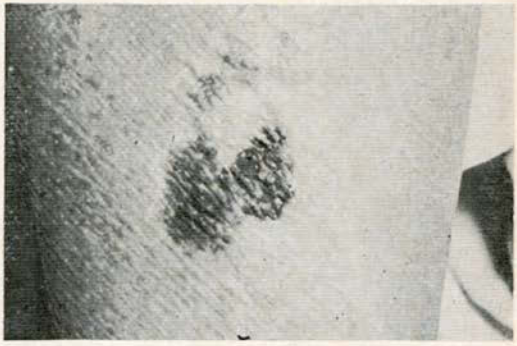

Fig. 2. Junctional naevus on the forearm of an elderly woman. It is smooth, flat, hairless and looks like a spreading drop of paint.

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†This work is supported by a grant for research from the National Cancer Institute of Canada.

The Ominous Changes

Almost any abrupt change in a mole may indicate malignancy, as may the sudden appearance of a mole in an adult where none was seen before.

The most common alteration noted by patients in our study was *an increase in size.* (Figure 3) Malignant transformation may be followed by not only an increase in diameter, but also by elevation of the lesion or by nodularity beneath the normal skin around the mole.

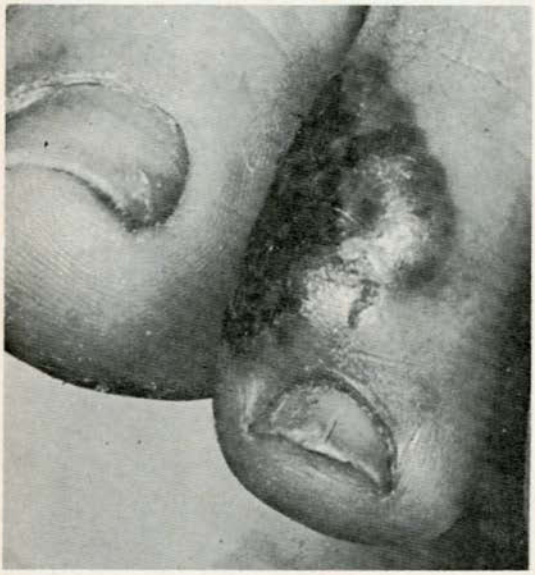

Fig. 3. Melanoma on the left second toe of a 67 year old woman. She had a mole here all of her life. Three months before she was seen, the mole began to increase in size, and to darken, became irritated, began to discharge, and bled on two occasions.

The second most common change in lesions that were proven to be melanomata was *bleeding.* Naturally patients tended to attribute bleeding to minor trauma, which delayed appreciation of its true significance.

The next most common changes are *ulceration, infection,* and *failure to heal. Itching, irritation, pain,* and the appearance of an *erythematous halo,* about a mole are common manifestations of malignant change and should alert the physician.

A *change in colour* may direct attention to a particular mole. Increased pigmentation of moles is normal with adolescence and pregnancy, but it may also be seen in moles that are becoming malignant. It may be better to remove one or two suspicious moles in a patient who notes increased pigmentation than to wait too long for confirmation that it is only a sign of a general endocrine alteration. A change in a portion of a mole to either a lighter or a darker colour is far more ominous; the recent appearance of a *variegated colour pattern* (Figure 4), especially if associated with other changes is almost pathognomonic of malignant change.

The appearance of *satellite pigment spots* about a mole is, of course, not only indicative of malignant change but of early lymphatic spread.

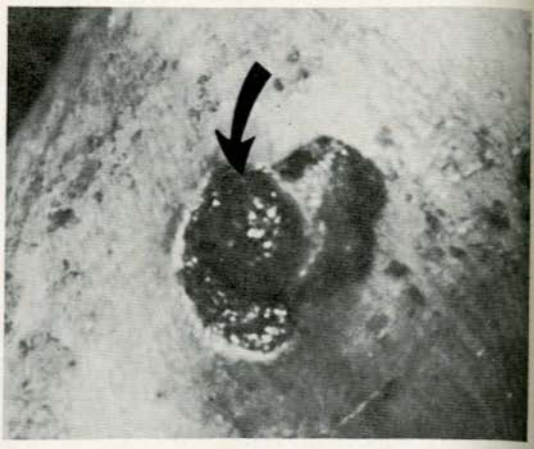

Fig. 4. Melanoma on the calf of a 78 year old man, where he had had a mole for many years. A few months before he was seen the lesion began to grow. A black junctional naevus may be seen at the periphery (upper right). A central, red, elevated dome (arrow) of tumour tissue made the diagnosis almost certain. An ill-advised incisional biopsy has been done (lower left).

Management of the Suspicious Lesion

Moles that have aroused suspicion should be dealt with by biopsy-excision, along with an adequate margin of normal tissue, under either local or general anaesthesia. Some melanomas are obvious from their clinical appearance, and in others the diagnosis will become apparent if one examines the regional nodes and the skin over the lymphatic pathways draining the lesion; in these instances the problem is one of management of the primary rather than of diagnosis.

Above all, THE SUSPICIOUS LESION SHOULD NOT BE CAUTERIZED with a Hyfrecater. No mole, in fact, should ever be treated by electrodessication. It has been known for many years that if a mole is malignant and if it is cauterized, viable tumour cells will be disseminated along lymphatics in almost 100% of cases[3].

In addition, INCISIONAL BIOPSY IS TO BE CONDEMNED. It is true that in rare instances there may be no alternative, but the risk of cutting into a pigmented lesion, should it prove to be malignant, is considerable.

The best approach to a biopsy of a mole is to plan the procedure so that there will be no regrets should the lesion prove to be malignant. Ideally one would like to take one or even two centimetres of normal skin around the lesion, but admittedly one must at times settle for a few millimeters. Melanoma is a three-dimensional growth, and one must be deep as well as wide of the tumour.

Adequate biopsy implies a sizeable defect to be closed. This can be done by wide undermining.

rotation flaps, or simply a graft. To me a grafted excision site is the signature of an adequate biopsy. It will be apparent that a proper diagnostic biopsy of a suspicious mole is often better done in an operating room and under general anaesthesia.

Management of Proven Melanoma

Once the diagnosis of malignant melanoma is established histologically, a thorough search for distant spread must be carried out, if this has not been done previously. Regional lymph nodes, lungs, liver, cancellous bone, skin, and subcutaneous tissues, all common sites of metastases, must be examined clinically and radiologically. There is no point in attempting treatment "for cure" in the patient whose tumour has spread beyond the primary site and regional lymph nodes.

In most instances the primary site will require wider excision, the block of tissue including the deep fascia this time, and the defect being covered by a graft. The amount of tissue to be excised is a matter of judgment, and no definite rules can be laid down. It is necessary to point out that if a diagnosis of frankly malignant, invasive melanoma has been made, the decision as to adequacy of excision must be made chiefly on clinical grounds. The pathologist can only say that the tumour does not extend to the edges of the specimen in the slides examined. In a number of the cases which we reviewed, the pathology report stated that excision was adequate, but early local recurrence followed. On the other hand, a pathologist's observation about inadequacy of excision should be taken seriously. For subungual melanoma, amputation of a digit may be necessary for adequate local excision.

As a rule treatment of malignant melanoma with the expectation of achieving a "cure" should include excision of the regional lymph nodes; exceptions may be made in elderly and debilitated patients and for some very superficial lesions. If the pathologist has given you a diagnosis of "superficial melanoma", you should have a talk with him and determine his concept of the aggressiveness of the tumour in question. Superficial melanoma has a better than average prognosis, but some superficial melanomas do metastasize and do kill patients.

The question of removing clinically negative regional nodes is admittedly controversial. A significant proportion of such nodes do contain tumour cells however, even some, we suspect, which are reported to be negative on routine histological examination. It may be that many patients with metastases in regional nodes also have blood-borne metastases which are not apparent, but to deny them regional node dissection is to adopt a philosophy of despair and therapeutic nihilism.

Surgeons argue with enthusiasm whether regional nodes should be removed in continuity with the primary, synchronously with excision of the primary or as a delayed procedure, but these issues are probably not decisive. What does matter is that the primary site be widely and adequately excised and that the regional node dissection be thorough.

When the malignancy is locally advanced, when there are metastases between the primary tumour and the regional nodes, or when regional lymph nodes are extensively involved, then limb perfusion, amputation, or even quarterectomy may be necessary. Surgeons are understandably reluctant to carry out mutilating procedures, and in the 135 cases which we reviewed, very few quarterectomies were done at a stage when there was any reasonable expectation of a cure. More frequent resort to such radical extirpation might have improved results in some instances. In addition, there are a variety of situations requiring special therapeutic approaches, including systemic metastases calling for palliative management, discussion of which is beyond the scope of this paper.

Prognosis

The outlook for the patient with malignant melanoma is certainly guarded but is by no means hopeless. Based on analysis of our experience in Nova Scotia, it appears that if a patient has no evidence of systemic disease beyond the regional nodes when he is first seen, he has about a 33% chance of being alive in 5 years and an 18% chance of being alive in 10 years. This is a poorer outlook than that of the patient with carcinoma of the breast, but it is better than the prognosis for carcinoma of the stomach.

Factors beyond our control, "biological predeterminism" if you like, are a dominant influence in the prognosis in any given case of malignant melanoma. Nevertheless proper medical management, including *early* recognition of the signs of malignant change in a mole, excisional biopsy, adequate local removal of the proven malignancy, and thorough extirpation of the regional lymph nodes, does result in a 5-year disease-free survival in this Province of about 55%.

Recent Advances

One would think, somehow, that a skin cancer, growing in plain sight on the surface of the body, ought to have a better prognosis than has malignant melanoma. The requisites of proper medical management, as outlined above, appear to provide only part of the answer to the problem.

Malignant melanoma kills by metastases, and it tends to spread early, especially by way of lymphatics. As the tumour invades the dermis, which it does in its initial stages, it has ample opportunity to permeate the rich dermal lymphatic plexus. From here clumps of tumour cells break off and embolize to regional nodes, where they lodge and grow, and less often to sites along the course of the lymphatic vessels themselves.

In a number of centres over the world[4-8] there has been a growing interest in treating lymph node malignancies, both primary and secondary, by lymphatic cannulation and intralymphatic injection of radioactive materials. The technique is similar to that used for a venous cutdown, except that the vessels are extremely small (Figure 5). We have chosen colloidal radioactive gold as a suitable material for intralymphatic administration, because the colloidal material adheres to lymphatic endothelium and is filtered and retained by the regional nodes. Beta particles, given off by the radiogold, have a range of only 3 or 4 millimeters and are able to irradiate the lymph vessels and nodes, and small tumour deposits in them, without appreciable effect on the overlying skin.

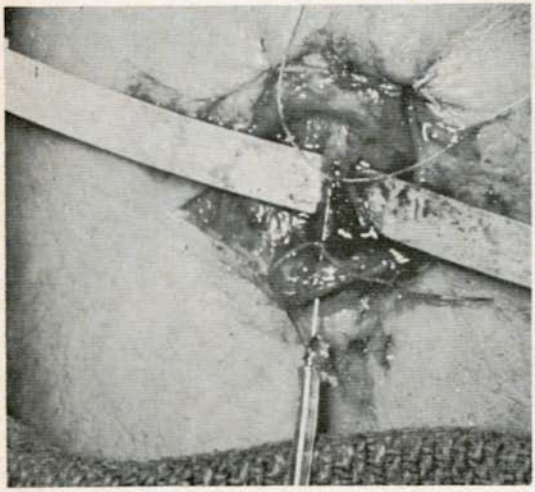

Fig. 5. A cannulated lymphatic. A transverse incision was made under local anaesthesia on the dorsum of the wrist. A lymphatic vessel was elevated on a mask wire and a No. 30 needle, attached to a plastic catheter, was passed into the lumen and secured with cotton ties. Radio-opaque dye or radioactive gold may now be given.

In a joint study by the Departments of Surgery and Radiotherapy of the Victoria General Hospital, and after preliminary animal investigation, fourteen intralymphatic injections of colloidal radiogold have been carried out in patients, seven of them for malignant melanoma, over the past 18 months. These have been done without local mishap or discernable evidence of systemic radiation effect, and in some cases radiation doses in excess of 50,000 rads to regional nodes have been achieved.[9] While melanoma is considered to be radioresistant, such resistance is relative, usually to the tolerance of the skin, and these doses are far in excess of what could be given through the skin by cobalt or high voltage X-ray. At the present time we regard intralymphatic radiotherapy as only an adjunct to the traditional surgical treatment described above. While our present interest centres about the feasibility and safety of the procedure, and it is much too early

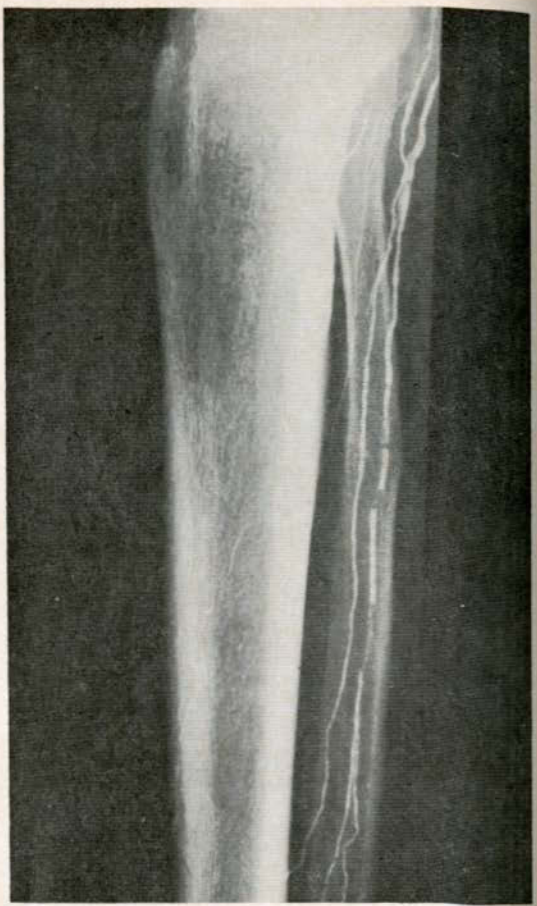

Fig. 6. X-ray of leg following injection of radio-opaque dye into a lymph channel in the foot. Such monitoring films must always precede administration of radioactive gold.

to begin to assess our results, we cannot help but suspect that some of our patients have benefitted from the very large amount of radiation placed in their lymphatic vessels and lymph nodes by this means. Clarly something should be done to improve our results, and we hope that intralymphatic administration of colloidal radiogold will contribute in some small measure to this end.

Summary

If patients with malignant melanoma are to have a more favourable prognosis, they must have the benefit of early diagnosis and adequate surgical therapy. The principle features by which malignant melanoma and its precursor, the junctional naevus, can be distinguished from harmless moles are enumerated. Biopsy must always be excisional. Adequate therapy includes wide local excision plus thorough regional lymph node dissection. A new approach to the problem of early lymphatic dissemination, by means of intralymphatic administration of radioactive colloidal gold, appears promising in the clinical trials now under way.

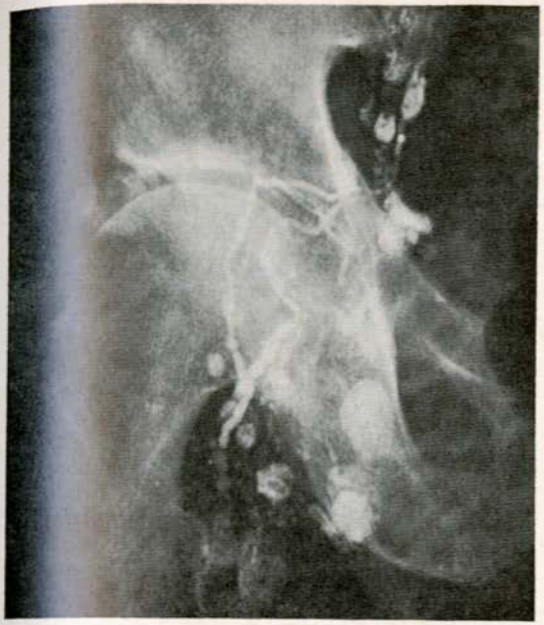

Fig. 7. X-ray of pelvis following injection of radio-opaque dye and colloidal radiogold. The opacified inguinal and iliac nodes are clearly seen. Note the beaded appearance of the pelvic lymphatics due to numerous valves. □

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Epidemics of Tuberculosis

In a review of reports of 109 tuberculosis epidemics in 12 countries, adults were found to be the usual source of infection. None of the epidemics was caused by children with primary tuberculosis. Identification of the source case is essential to control of the epidemic.

A review of 109 epidemics of tuberculosis in 12 countries, 84 (75%) of which were in schools, permits of certain generalizations about tuberculosis epidemics.

Any outbreak of tuberculosis results from a combination of circumstances. First, a large proportion of the group of individuals exposed to tuberculosis must be tuberculin negative. This state is usually associated with a lack of acquired immunity and is seen particularly in young children or in older individuals living in geographic areas where the tuberculosis rate is very low. The second factor is the presence of an individual who is a disseminator of tubercle bacilli, almost invariably an adolescent or adult with pulmonary tuberculosis.

The sputum of the disseminator usually contains many tubercle bacilli which can be detected on direct examination. Culture of the sputum yields a high colony count. In patients from whom the bacilli can be recovered only by culture, there are usually fewer colonies. Such patients are less likely to be contagious and are therefore harder to identify as the source of epidemics.

However, all patients with large numbers of living tubercle bacilli in their expectorations may not be of the same degree of contagiousness. It has been reported that the number of bacilli a patient discharges into the atmosphere depends not only on the number of bacilli in his sputum, but also on the fluidity of the sputum, the frequency and forcefulness of coughing and sneezing, and such factors as whether or not the patient covers his mouth when coughing.

Edith M. Lincoln, M.D. *Advances in Tuberculosis Research*: Karger, Basel/New York, 1965.

An example of this was the rapid spread of tuberculosis in a military band in Great Britain. A 23-year-old clarinet player was found to have infected eight other persons connected with the band who developed active pulmonary tuberculosis.

Members of bands appear to exhale more air than the average person and with much greater force, probably keeping droplets airborne for a longer time, and producing a greater concentration of airborne bacilli.

Adults are Source of Infection

Most epidemics are traceable to adults with contagious tuberculosis. In schools the sources are usually teachers, but may be a bus driver or custodian, a cook or some other person who comes in close, even if brief, contact with the pupils. Many school epidemics also have been ascribed to older children or to adolescents with chronic pulmonary tuberculosis.

The potential contagiousness of children with primary tuberculosis has been questioned for many years. A child with recent pulmonary primary tuberculosis may be assumed to have a few tubercle bacilli in a gastric lavage. The question is whether this means that the child is contagious. Children with nonprogressive pulmonary tuberculosis rarely cough, and they do not expectorate. Therefore, they probably do not disseminate tubercle bacilli into the atmosphere. Many pediatricians have seen children with nontuberculous pulmonary disease spend months or years in hospitals with tuberculous children and not develop a reaction to tuberculin. In the present review there was not a single report of a school epidemic caused by a child with primary tuberculosis.

Another important factor in the production of epidemics is the environment in which the contact occurs. Overcrowding and lack of ventilation increase the chances of infection.

Spotting the Epidemic

The early recognition of an outbreak of tuberculosis depends on how quickly the physician or health authority thinks of tuberculosis when a number of people in a small area have fever of unknown origin. Once tuberculin tests and subsequent chest X-rays are positive, the presence of an epidemic becomes obvious.

Multiple cases of erythema nodosum have been of help in arousing suspicion. Although relatively rare today, erythema nodosum is still a valuable guide to an epidemic of tuberculosis. Often epidemics are suspected as a result of finding a sudden increase in the number of tuberculin reactors in a community.

Most recognized epidemics develop in an incredibly short time. In one Norwegian village, an itinerant juggler caused 54 infections within a month. In such instances, it is clear that the exposed population has little or no acquired immunity and that the individual who is the source of infection has numerous bacilli in his sputum.

The first concern of the physician faced with an epidemic of tuberculosis should be to identify the source case. In schools this should not be difficult if all the personnel and older students are surveyed by tuberculin tests and by chest X-rays of all reactors. If the source is not found, the search must be continued outside the immediate classroom.

An adult or adolescent with active chronic pulmonary tuberculosis should be sent to a hospital or sanatorium for adequate therapy. An adolescent with pulmonary tuberculosis should not return to school until his disease is stabilized and cultures of sputum have been negative for three to six months.

Caring for the Child

A child with symptomatic primary tuberculosis should be treated at home or in a sanatorium according to his medical needs and the ability of his family to give him adequate care at home. Students with asymptomatic primary tuberculosis should be allowed to stay in school provided they remain under medical supervision and take isoniazid daily for at least a year. The addition of PAS is a matter of opinion. Isoniazid is given primarily to prevent complications since no drug therapy is known to eliminate all tubercle bacilli from the body. Thus, following an epidemic all tuberculin reactors should have chest X-rays at yearly intervals for an indefinite period. Home contacts should also be examined.

The tuberculin test is the most valuable tool of tuberculosis control. It permits the classification of those who are uninfected and hence susceptible to infection and those who have been previously infected with tubercle bacilli. As the rate of infection decreases, tuberculin surveys, with chest X-rays only of reactors, may become the method of case finding in adults as well as in children. It is essential to follow all the individuals known to react to tuberculin, particularly in countries with a low incidence of tuberculosis. Only in this way can pulmonary tuberculosis be found early, when it is most amenable to treatment. □

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