THE VALUE OF B.C.G. VACCINATION IN CONTROL OF TUBERCULOSIS*

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Vaccination with B.C.G. is now so universally applauded that any attempt to question its value is regarded almost as heresy. Despite this I propose in this address to act as Devil's advocate, and to ask seriously whether the claims of Calmette and Guérin to canonization rest on an unshakable foundation. So far, B.C.G. vaccination has not been used in Great Britain, but there is an increasing demand from tuberculosis workers for its introduction. Before this step is taken let us be sure that it is fully justified. It is much easier to introduce a given measure into the public health practice of this country than to remove it once it has become firmly established. On a more suitable occasion I may dilate on what I call "public health anachronisms"—practices that are carried on now because they have been in use for the last thirty years or so, even though it has since been shown that they are of little or no value for the purpose for which they were originally intended. The accumulated weight of precedent is almost overpowering, and I therefore ask you to pause for a moment before committing yourselves to a practice that it may be very difficult subsequently to discontinue.

Let me make it clear that I have no prejudice either in favour of or against B.C.G. vaccination. I am merely interested in learning the truth about it. The published evidence, however, that I shall review briefly leads me to the conclusion that, though a strong presumptive case may be made out for the value of B.C.G., it is not yet convincing enough to justify the whole-hearted acceptance of this agent as a means of preventing tuberculosis in Great Britain.

Vaccination of Infants with B.C.G.

Of the numerous investigations reported on the vaccination of infants with B.C.G. the majority have included no control group. Attempts to assess the value of the procedure have been made by comparing the tuberculosis death rate among the vaccinated infants with that among the infant population as a whole, either during the same period or during the previous five years or so, or with a group of ostensibly similar infants which have not been offered vaccination. Calmette (1928), for example, vaccinated one group of infants and compared the mortality among them with that among children of tuberculous parents and other children who were exposed to massive infection in their first year of life. As Greenwood (1928), however, pointed out, there were gross fallacies in these figures, and the comparison that Calmette made between the mortality in the vaccinated infants and that in the non-vaccinated was quite unjustifiable.

Wallgren (1934), working at Gothenburg, vaccinated every infant that was considered by the municipal dispensary to be in danger of infection from family contact. The result was striking. The infantile tuberculosis death rate fell from 3.9 per 1,000 in 1927, the year before this routine was introduced, to 0.3 per 1,000 in 1933—a fall of 92%. But, as Wallgren is the first to point out, it is impossible to assess the part played by B.C.G. in this achievement. The infants, for example, were separated from their parents for a variable period of time after vaccination, and in some instances were not exposed to infection till they were a year old. Moreover, the educational work of the dispensary nurses stimulated the interest of the mothers, so that they co-operated in shielding their infants from infection and made full use of the prophylactic means at their disposal. The ensuing fall of 92% in the infant mortality rate due to tuberculosis was almost certainly greater than any fall that might otherwise have occurred during the years 1928 to 1933. It is fairly safe to conclude, therefore, that the very thorough measures taken by Wallgren were mainly responsible for the result observed, but it is quite impossible to say what part in this result was played by B.C.G.

Chicago Investigation

Two lots of workers have included a special control group in their series. At Chicago, Rosenthal, Bland, and Leslie (1945) carried out an investigation at the Cook County Hospital. Expectant mothers desiring vaccination for their babies were asked to sign a consent card. X-ray studies were then made of the entire household to find out whether any of the members was suffering from tuberculosis. The child of every alternate mother who had consented was vaccinated with B.C.G. by the multiple-puncture method, usually when it was three to seven days old. The children were kept under observation and were tuberculin-tested and x-rayed at intervals.

The infants were divided into those having no contact with known cases of tuberculosis and those known to be exposed to contact. In the non-contact group 1,204 vaccinated children were observed and 1,213 control children. Among the former there were three cases of tuberculosis and one death, among the latter 23 cases and four deaths. In the contact group, infants who were in contact with closed cases of tuberculosis were removed from their homes for six weeks to three months; those who were in contact with open cases were permanently removed and kept in a foster-home. Among 98 newborn infants who were in contact with tuberculosis after vaccination there was one case of tuberculosis and no death; among 63 controls there were four cases and three deaths. Taking the

*A paper read at the International Conference of Physicians on Sept. 12.

contact and non-contact groups together, we see that there were four cases and one death in the vaccinated group as opposed to 27 cases and 7 deaths in the control group (Table I).

TABLE I.—*B.C.G. Vaccination of Infants in Chicago (Rosenthal, Blahd, and Leslie, 1945)*

Group	Subgroup	No. of Children	No. of Cases of Tb.	No. of Deaths from Tb.
Non-contact ..	Vaccinated	1,204	3	1
	Control	1,213	23	4
Contact ..	Vaccinated	98	1	0
	Control	63	4	3
Contact and non-contact together	Vaccinated	1,302	4	1
	Control	1,276	27	7

Superficially these results are impressive, but before accepting them at their face value one would like to have information on a number of points that are left vague. (a) The follow-up apparently did not start till three to seven months after vaccination, by which time it would seem that many infants in both groups had died; it would be interesting to know more about these infants, since they are completely ignored in the final figures; (b) the total deaths from all causes were 21 in the vaccinated and 21 in the control group, but, apart from those due to tuberculosis after the follow-up had started, there is no information on when they occurred or what they were due to; (c) it is said that observations were made on the non-contact group during a period of seven years and on the contact group during a period of three to four years, but it is not stated what was the average duration of observation among the vaccinated and the control groups; (d) there is no information on whether the radiologist who read the x-ray photographs knew whether the child had been vaccinated or not; (e) in the early part of the investigation on the contact group there were no controls; the vaccinated children during this period, however, are included in the comparison; (f) it is not clear whether in the contact cases the controls were isolated in exactly the same way and for the same length of time as the vaccinated.

The results of this investigation suggest that B.C.G. vaccination may lead to some lowering in the morbidity and the mortality rates in infants, but without more precise information on the method of conducting the investigation it would be unwise to regard this as more than a very tentative conclusion.

New York City Investigation

In New York City a more or less similar investigation was carried out, with results that are both interesting and illuminating. Observations were made on children in tuberculous families. Practically all children came under observation before they were a year old, and no child over one month old was accepted unless it was both tuberculin and x-ray negative. Except during the first two years of the trial, when the vaccine was given by mouth, all inoculations were made intracutaneously. After January, 1933, the B.C.G. dose was standardized at 0.15 mg. Between 1926 and 1932 the children were divided into two groups, according to whether the mother wished her baby to be vaccinated or not. Under these conditions the children of the more intelligent and co-operative parents tended to be vaccinated and those of the careless and less intelligent parents to constitute the control group. From 1933 onwards the mode of allocation into groups was altered. Consecutive mothers were asked whether they would like to have their children vaccinated. Those that refused were not considered any further. To the children of the mothers who were willing to accept vaccination B.C.G. was given alternately without selection. Under these conditions both the vaccinated and

the control groups comprised children who came from the same class of co-operative parents. The results of this investigation, as described by Levine and Sackett (1946), are given in Table II.

TABLE II.—*B.C.G. Vaccination of Infants in New York City (Levine and Sackett, 1946)*

Period	Alternate Selection	Vaccinated Group			Control Group		
		No. of Children	No. of Deaths from Tb.	Tb. Mortality %	No. of Children	No. of Deaths from Tb.	Tb. Mortality %
1926-32	No	445	3	0.67	545	18	3.30
1933-44	Yes	566	8	1.41	528	8	1.52

It will be observed that during the first period, when the method of selection was faulty, the tuberculosis mortality in the control group was five times that in the vaccinated group; but during the second period, when strict alternate selection was practised, the tuberculosis mortality in the two groups was almost identical.

These results serve to show how important it is, when carrying out a controlled investigation on human subjects, to do everything possible to ensure that the vaccinated and the control children are similar in every respect, including such factors as age, race, sex, social, economic, and housing conditions, intellectual level and co-operativeness of the parents, risk of exposure to infection, attendance at infant welfare or other clinics, and treatment when ill.

Levine and Sackett's findings are open to criticism on three points. First, no records are given of the morbidity, as opposed to the mortality, in the two groups. Secondly, the diagnosis of tuberculosis in 3 of the 11 fatal cases in the B.C.G. group was doubtful. It may be pointed out, however, that only one of these occurred in the 1933-44 period, so that even if this case was excluded it would not have much effect on the final results. Moreover, a similar deduction might have to be made for unconfirmed diagnoses in the control group, though the number of such cases is not stated. Thirdly, the most serious criticism is that the infants were not usually separated from their tuberculous parents before and after vaccination, with the result that some infants may have been actually infected before they were vaccinated and others may have been exposed to infection before immunity following vaccination had had time to develop. It is difficult, as the authors themselves admit, to know how much allowance to make for this factor. Any attempt to make such allowance would be largely guesswork. It is probably safer to conclude that, though B.C.G. vaccination of the infants of tuberculous parents might be of value if accompanied by the necessary amount of segregation to ensure that exposure to infection did not take place till immunity, as judged by the tuberculin test, had been established, under ordinary conditions in which the infants are brought up in a tuberculous environment it seems to confer little, if any, protection.

The results of this investigation do not support those of the Chicago experiment, and we are therefore left without any convincing evidence that B.C.G. vaccination of infants by itself confers any considerable degree of protection against the risk of death from tuberculosis in early life.

Vaccination of Nurses with B.C.G.

The two main investigations on the B.C.G. vaccination of nurses are those of Heimbeck (1936) in Norway and of Ferguson in Canada (1946). Since Ferguson included no control group in his series, and merely judged the efficacy of the B.C.G. vaccination by a diminution in the tuberculosis morbidity of nurses during the investigation in

relation to that in nurses during the previous 5-year period, his results, however suggestive, cannot be accepted without question. It is impossible to be certain that the conditions during the period of the investigation were identical with those before vaccination was started, and conclusions drawn from comparisons of this sort are liable to be misleading.

Of Heimbeck it is probably true to say that he has done more than any other single person to convince tuberculosis workers of the value of B.C.G. vaccination in protecting against the disease in young adults. His conclusions are based on two main contentions: (a) that tuberculin-negative nurses are more liable than tuberculin-positive nurses to contract tuberculosis; and (b) that among tuberculin-negative nurses vaccinated with B.C.G. the tuberculosis morbidity is lower in those who become tuberculin-positive as the result of vaccination than in those who do not.

Heimbeck's work was carried out on probationer nurses entering the Ullevål Communal Hospital at Oslo during the years 1924 to 1935. Every nurse was submitted to a von Pirquet test on entry. This was repeated periodically on those that failed to react. From 1927 onwards the negative reactors were vaccinated subcutaneously with B.C.G. As a result rather over two-thirds became von Pirquet positive. The two groups were followed up for two to three years, and the number of cases of tuberculosis developing was noted. The results given in Table III are restricted to cases of pulmonary tuberculosis, the multiple minor manifestations, including erythema nodosum, being omitted.

TABLE III.—*B.C.G. Vaccination of Nurses in Oslo (Heimbeck, 1936)*

Group	Subgroup	No. of Nurses	Nurse Observation Years	No. of P.T. Cases	Rate per 1,000 Observn. Years
von Pirquet positive on entry	(a)	625	2,659	4	1.5
von Pirquet negative on entry	(b) Not vaccinated	280	561	13	23.2
	(c) Vaccinated and became positive	287	910	1	1.1
	(d) Vaccinated and remained negative	107	204	1	4.9

P.T. = Pulmonary tuberculosis.

It will be seen first of all that the nurses in subgroup *b*, who were von Pirquet negative and were not vaccinated, suffered much more heavily from pulmonary tuberculosis than those in subgroup *a*, who were initially von Pirquet positive. The difference between groups *c* and *d* is very much less, and by the ordinary statistical tests would not be regarded as significant.

Before regarding the difference between groups *a* and *b* as conclusive two points must be noted. In the first place the girls had been subjected to a careful medical examination before being accepted as probationers, and any girls with a history of tuberculous disease or showing evidence of tuberculosis were rejected. The effect of this would be to reduce the number of subjects in group *a* who developed pulmonary tuberculosis during their training period. Secondly, instead of following up initially positive and initially negative nurses over the same length of time, Heimbeck transferred in his analysis the initially von-Pirquet-negative nurses to the positive group within one year of their primary infection. The result was that if the nurse developed symptoms of tuberculosis within a year of her primary infection she appeared among the initially negative group that became tuberculous. If, on the other hand, she showed no evidence of tuberculosis for a year or more she went to swell the number of the initially von-Pirquet-positive group that remained free. Since the majority of tuberculous lesions in initially tuberculin-negative nurses seem to occur during the year following the appearance of a positive reaction (Israel, Hetherington,

and Ord, 1941; Daniels, 1944), the effect of this transfer must have been to increase the disparity between the two groups and weight the odds in favour of the initially tuberculin-positive group. (It is a little doubtful how the groups were finally constituted, but in this account I have adhered strictly to that given in Heimbeck's paper).

Vaccination of Primitive Peoples with B.C.G.

Starting in 1935, a carefully controlled study, lasting for six years, was made by Aronson and Palmer (1946) among North American Indian children and young adults. The subjects, who ranged from 1 to 20 years of age, were tuberculin-tested with P.P.D. (purified protein derivative). Those who failed to react to 0.005 mg. were divided at random into two groups.

The first group, which comprised 1,550 persons, were injected intracutaneously with 0.1 or 0.15 mg. of B.C.G.; the second group, which comprised 1,457 persons, were injected with 0.1 ml. of sterile saline. An initial x-ray film was taken to exclude those with evidence of pulmonary tuberculosis, and the inoculated subjects were re-examined annually by the tuberculin test and by radiography. The expert who read the x-ray films did not know to which group any given subject belonged. Analysis showed that the two groups were very similar in age, amount of exposure to tuberculous infection, and completeness of the follow-up. The results are summarized in Table IV.

TABLE IV.—*B.C.G. Vaccination of North American Indian Children and Young Adults (Aronson and Palmer, 1946)*

Group	No. of Subjects	No. Developing N.P.T.	No. Developing P.T.	Tb. Case Rate per 1,000 Person-years*	No. of Deaths from all Causes	No. of Deaths from Tb.
Vaccinated	1,550	9	8	2.0	34	4
Non-vaccinated	1,457	48	20	9.0	60	28

* Pleural effusion and hilar gland enlargement excluded.

As in the record of Heimbeck's investigations, I have purposely omitted cases of pleural effusion and enlarged hilar glands from the pulmonary tuberculosis figures so as to make the comparison between the vaccinated and control groups more definite. It will be noted from Table IV that the incidence of pulmonary, and still more of non-pulmonary, tuberculosis was considerably higher in the group receiving saline than in that receiving B.C.G., and that the tuberculosis mortality was seven times as high in the control as in the vaccinated group.

These figures are very suggestive, but it may be questioned whether the conclusions drawn from them can legitimately be transferred to civilized peoples having a higher degree of genetic immunity and exposed, as a rule, to a lower risk of infection. Some indication of the lack of similarity between the North American Indians and the ordinary population of the United States is afforded by the great difference between them in the incidence of non-pulmonary tuberculosis. In Aronson and Palmer's control group, for example, the ratio of non-pulmonary to pulmonary tuberculosis was about $2\frac{1}{2}$ to 1, whereas in the United States as a whole, during the years 1935-41, the ratio among persons of 1 to 25 years of age, as judged by the recorded deaths (figures for incidence not available), was about 1 to 5. It is, in fact, doubtful whether the same proportionate degree of protection is likely to be conferred by vaccination in a community such as our own as in a race of people in which the natural history of tuberculosis is so very different. In this connexion it may perhaps be well to remember the law of diminishing returns.

Discussion

Within such a short compass as is here allowed it is impossible to do justice to the full claims for B.C.G., but I have selected for review those investigations which come more closely to a controlled laboratory experiment than any others. Even so, it must be admitted that the results of all but one of these investigations are inconclusive. What we have got to decide is whether the routine use of B.C.G. in this country would diminish the total tuberculosis incidence and mortality. It is clearly impossible to estimate numerically the advantage that such a course would have, or even to be sure that it would have any advantage at all. Assuming, however, that B.C.G. does afford some measure of protection against the development of clinical tuberculosis, let us consider the difficulties and disadvantages that its use might entail.

(1) B.C.G. is a live vaccine, and should be used within a week of its preparation. This means that very great care has to be taken in its preparation to avoid contaminants, and in its distribution to make sure that a high proportion of the organisms are alive at the time of injection. (2) The virulence of B.C.G. is not fixed. If it is too virulent harmful reactions may occur in those who are injected; if it is not sufficiently virulent the degree of protection it affords will be reduced. (3) The injection has to be made intracutaneously with considerable care. If the vaccine is injected too deeply serious ulceration may occur at the site of injection in a high proportion of subjects and persist for weeks or months, sometimes accompanied by suppuration of the regional lymphatic nodes. Even if the injection is made strictly into the superficial layers of the skin a small local ulcer may normally be expected to develop (Holm, 1946). It is true that some of the disadvantages of intracutaneous injection are said to be avoided by the multiple-puncture method (Birkhaug, 1944), but too little experience of this method is as yet available to justify the claims of its author. (4) The infants of tuberculous mothers must be separated at birth, or, if taken away at a later age, they must be separated for at least six weeks to exclude the possibility of their having already acquired tuberculous infection by the natural route before they can be vaccinated. (5) After vaccination they should be separated from their parents for two to three months in order to allow a reasonable degree of immunity to develop. (6) Infants separated in this way and kept in residential nurseries may be exposed to serious risk of cross-infection, and develop pneumonia or gastro-enteritis, either of which may prove fatal. (7) Since the B.C.G. organisms die out in the human body, it is desirable to revaccinate the child at intervals to ensure the continuance of immunity.

Taken individually, none of these disadvantages need be regarded too seriously, but taken together they do combine to render B.C.G. vaccination very much more formidable than vaccination against smallpox or diphtheria. Even if it is assumed that B.C.G. is of value it must be asked whether it should be applied to the whole population or only to selected portions of it. When it is realized that in England and Wales the chances of dying from tuberculosis in the first year of life are 1,740 to 1 against, I think we may conclude that universal vaccination of the infant population is out of the question. If it was pressed it would almost certainly result in the partial substitution for highly reliable prophylactic procedures, such as vaccination against smallpox and diphtheria, of the very much more doubtful procedure of B.C.G. vaccination, since a considerable proportion of parents would refuse to have their children inoculated with all three agents—particularly if the B.C.G. vaccination, which would normally be given first, was followed by any serious local disturbance. The alternative, therefore, would be to restrict B.C.G. vaccination to those groups of the community, such as the infants and children of tuberculous families, and medical students and

nurses, who are exposed to an unusually high risk of developing tuberculosis (see Cox, 1929; Ridehalgh, 1942; Daniels, 1944). If it is adopted for these groups, then infants and children should be separated for a time from their tuberculous parents for the reasons that have already been stated, and care should be taken that medical students and nurses are kept away from any known source of tuberculous infection for six to twelve weeks after vaccination.

Before we commit ourselves to adopting this course it would be of great help if a properly controlled investigation on human beings could be carried out in this country. The difficulties of such a task are not underestimated, but unless we do attempt to measure the advantage so gained we shall never know the real value of B.C.G. vaccination, and we may not even know whether it is of any value at all in the circumstances in which we use it. It is suggested that a suitable trial might be carried out on probationer nurses entering the London and larger provincial hospitals. The results of the Prophit investigation (Ridehalgh, 1942; Daniels, 1944) have shown that about 20% of these nurses are tuberculin-negative at the start of their training course. Forty thousand nurses should therefore include 8,000 who are suitable for investigation. Alternate tuberculin-negative nurses should be vaccinated with B.C.G. and the remainder should receive some control fluid indistinguishable in appearance from it. If 0.5% of the nurses in the control group develop pulmonary tuberculosis annually, and if the average period of follow-up is two years, the number of cases in this group should amount to 40. If the B.C.G. vaccination is really effective the number of cases in the vaccinated group should be small enough to render the difference between the two groups significant. It is realized, of course, that the 40,000 nurses required initially for testing could not be obtained at once, but if 4,000 to 8,000 were taken into the investigation every year an answer should be forthcoming in about five to ten years.

In an investigation of this sort I feel that the comparison between the two groups should be confined to pulmonary tuberculosis of reasonable severity. I shall not attempt to define this more accurately now. My point is that if minimal pulmonary, glandular, and other manifestations of tuberculosis are included it may be possible to swell the number of tuberculous cases in the control group, as in Heimbeck's (1936) figures, and make out a theoretically convincing but practically unimportant case for B.C.G. vaccination. Should such a properly controlled trial prove impracticable, then I would suggest that B.C.G. vaccine should be liberated for use only under strictly defined conditions ensuring the most careful follow-up of the vaccinated subjects with some degree of central supervision.

If B.C.G. vaccination is to be undertaken the gains must be commensurate with the disadvantages; and unless it can be shown that the morbidity and, particularly, the mortality from tuberculosis are substantially lowered I should regard it as doubtful whether routine vaccination of all tuberculin-negative nurses and medical students was worth while adopting. When it is realized that during the whole of the Prophit survey, which lasted for ten years, only two nurses died from tuberculosis, giving an annual mortality rate one-third of that for the female population of corresponding age in England and Wales, it may be wondered whether the relative degree of immunity that B.C.G. vaccination may possibly confer is likely to be of any substantial value in practice, and whether almost equally good results might not be achieved by measures designed to protect nurses from undue exposure to infection.

Infants and children in tuberculous families present a rather different problem. Presumably the best answer, as a rule, is to remove the tuberculous member of the family from the house; but if this is not practicable the children should be removed. This has got to be done temporarily in any case if they are to be vaccinated, as all the protagonists of B.C.G. insist that separation for a time is necessary if the best results are to be obtained. If temporary removal has got to be practised, it is surely worth while considering whether separation should not be continued till the tuberculous member of the family has been cured, has died, or has been admitted to an institution for chronic cases.

One more word. Is it really worth while vaccinating infants at birth? We are still ignorant of the time the antibody-producing mechanism takes to reach maturity, but we have reason for believing that the tissue response to antigenic stimuli during the first few months of life is less than it is by the end of the first year. That is why inoculation against diphtheria is usually delayed till nine to twelve months after birth. Is there any reason for believing that the tissue response to a vaccine against the tubercle bacillus is likely to be more active than that against other antigens? If not, would it not be better to remove the infant from its tuberculous home at birth and delay vaccination with B.C.G. till it is at least 6 months of age? That this objection is not purely hypothetical is borne out by the finding that infants at birth require larger doses of B.C.G. than older infants to render them tuberculin-sensitive, and take a longer time to become allergic (Wallgren, 1947).

Summary and Conclusions

Investigations are reviewed in which a control group of persons was studied along with a B.C.G. vaccinated group.

Though a presumptive case for the value of B.C.G. vaccination has been established, it is concluded that the documentary evidence so far available is insufficient to allow any estimate to be made of the degree of protection it affords or even to prove conclusively that, in a civilized population, it has any protective effect at all.

Some of the disadvantages of B.C.G. are enumerated, and it is argued that, unless the gains from its use are likely to be substantial, B.C.G. vaccination in this country may not be worth while undertaking.

Since the risk of dying from tuberculosis in the first year of life is so small, universal vaccination of infants is clearly out of the question, and vaccination, if it is used, should be restricted to specially exposed groups, like nurses, medical students, and children in tuberculous families.

It is pointed out that the tuberculosis mortality among nurses in the Prophit survey was only a third of that among the corresponding female population in England and Wales; and it is doubted whether the relative degree of immunity that might be conferred by B.C.G. vaccination would have any greater effect in lowering the mortality than measures designed to shield nurses against undue risk of exposure to tuberculous infection.

It is further pointed out that infants and children of tuberculous parents must be separated from their homes for two to three months after vaccination with B.C.G. in order to allow immunity to develop; and it is questioned whether it might not be wiser to prolong this separation till the infecting member of the household has been cured, has died, or has been removed to an institution for chronic cases.

Since the normal antibody-producing mechanism does not seem to reach maturity till towards the end of the first year of life it might be better, if B.C.G. is to be used, to remove the infant from its tuberculous home at birth and delay vaccination with B.C.G. till it is at least six months of age.

A plea is entered for the carrying out of a properly controlled trial of B.C.G. vaccination in Great Britain, or, if this

is impracticable, for the liberation of the vaccine only under strictly defined conditions.

I am indebted to Prof. A. Bradford Hill for help in assessing the evidence in some of the investigations reviewed in this paper.

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SYMPATHECTOMY AND INTRASPINAL ALCOHOL INJECTIONS FOR RELIEF OF PELVIC PAIN*

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Pain may be either acute or chronic. In women acute pelvic pain is not infrequent, and may be due to such causes as rupture of an ectopic pregnancy or of a corpus luteum cyst, or sudden torsion of an ovarian cyst. Such causes of pain may be relieved instantly and dramatically by a surgical operation. Likewise, in many cases in which the pain is chronic, as in pelvic inflammatory disease and endometriosis, an operation that removes the source of the pain brings relief. However, there are many women who suffer severe pain and in whom removal of its cause is either impossible or inadvisable. In this category are women with inoperable carcinoma of the uterus or severe dysmenorrhoea, women subjected to repeated unsuccessful laparotomies for the relief of pelvic pain, and young women with endometriosis who should not be castrated.

For the intractable pain associated with carcinoma of the uterus, particularly of the cervix, most physicians prescribe an opium derivative such as morphine, "pantopon," codeine, or "dilaudid." These drugs are temporarily helpful, but eventually the patient becomes refractory to them. The reasons for this inadequacy are: (1) the potential tolerance for the drugs increases enormously, so that larger and larger doses are required, resulting in a constant increase in expenditure for the drugs until the poor patient can no longer afford them; (2) in some people the opium derivatives produce nausea and vomiting; and (3) a few individuals become drug addicts.

To secure more or less permanent relief from the excruciating pain which is associated with cancer of the uterus, severe dysmenorrhoea, endometriosis, and the distressing pain of unknown origin, I recommend two useful procedures. The first is pelvic sympathectomy, or removal of that part of the sympathetic nerve plexus known as the presacral nerve or the superior hypogastric plexus. The second is intraspinal injection of alcohol.

*Read before the Oxford Postgraduate School of Medicine on July 14, 1947.