then to produce total arrest by clamping the superior and inferior venae cavae, the aorta, and the pulmonary artery. At the end of the agreed period the clamps are released, the wound is closed, and the animal's progress is watched. In successive experiments the period of arrest has been lengthened. It will be seen that in the control dogs (hypothermia at one-atmosphere pressure of oxygen) the maximum safe period of cardiac arrest is about 20 minutes. Up to that point there has been no difficulty in getting the heart restarted, and the dogs have survived permanently with no neurological or other sequels. Of the five dogs in which cardiac arrest at normal pressure was maintained for 25 minutes, two could not be restored at the end of this period, and one other dog developed slight ataxia which persisted for two days. By contrast, in the dogs treated in the

chamber at two-atmospheres pressure a period of arrest of 30 minutes was well tolerated and one dog survived even as long as 40 minutes.

At the present time further experiments are in progress to determine the minimum circulatory flow rate necessary to raise the period of cardiac arrest to one hour or more. It is hoped that in this way it may be possible to simplify the technique of artificial circulation in open heart surgery.

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PREVENTION OF VIRUS DISEASES IN THE COMMUNITY*

BY

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The control of infectious diseases depends mainly on the production of immunity by vaccines, and on epidemiological control—with the identification, quarantine, and treatment of infected individuals. The balance between the usefulness of these two methods—vaccination and epidemic control—varies from a disease like typhoid, where (in the United Kingdom) we rely exclusively on epidemic control, to a disease like poliomyelitis, where, at least for the next few years, we shall have to rely largely on immunization.

One of the great heresies about immunization is that epidemics of a particular disease will cease when about 75% of children have been immunized against it. It has been said, for example, that "For adequate protection of the population against epidemic spread of smallpox, at least 75% of infants should be vaccinated" (Ministry of Health, 1956). This is not true, for in the past extensive outbreaks of smallpox occurred in Britain at a time when there was at least 75% acceptance of infant vaccination, and in many places 75% of the susceptible population have been naturally immunized by infections of smallpox, poliomyelitis, and other viruses and yet outbreaks of these diseases occurred and continued to occur.

Risks Associated with Smallpox Vaccination

In any immunization programme we must be quite sure that the risks associated with immunization are less than the risks of contracting the disease. I would like to consider this in relation to smallpox vaccination, the main risks of which are generalized vaccinia and post-vaccinal encephalitis. How common are these? How often are they fatal? *Unfortunately it is impossible to obtain accurate data on this.*

The available figures (Table I), which are not very reliable, give the mortality from primary vaccination in England, Wales, Scotland, and part of Northern Ireland for the period 1951 to 1958.

It seems probable that deaths from vaccination are often not reported; there is no obligation to do so and,

furthermore, some doctors may not report that vaccination has injured or killed a baby if he has persuaded the parent to accept it, and if he has always thought that vaccination was a safe procedure. It is our duty to measure the danger of vaccination, but unfortunately, and perhaps we all share some blame, this has not been carefully done. Can we do anything about this?

TABLE I.—Mortality Per Million Primary Vaccinations—England and Wales, Scotland, and Part of Northern Ireland (1951–8) (Griffith, 1962)

Complications	Age-group, Years			
	<1	1–4	5–14	15+
Generalized vaccinia ..	4.7	0	0	0
Post-vaccinal encephalitis ..	9.0	0	0	5.3
Others ..	1.7	1.9	0	0
Total ..	15.4	1.9	0	5.3

It is often suggested that vaccination is best done in infancy because it will prevent complications when revaccination is carried out in later life for travel or military service. The published figures (Table II) show that the total mortality from primary vaccination in infancy plus revaccination at 15+ is 18.4 per million compared with 5.3 if primary vaccination is done in

TABLE II.—Complications and Mortality Per Million of Primary Infant Vaccination Plus Revaccination at 15 Years and Over, Compared with Primary Vaccination at 15 Years and Over (Dixon, 1962). Data from England and Wales, Scotland, and Part of Northern Ireland (1951–8)

Complications	Primary Vaccination in Infancy plus Revaccination at 15+		Primary Vaccination at 15+	
	Complications	Mortality	Complications	Mortality
Generalized vaccinia ..	58.8	4.7	76.9	0
Post-vaccinal encephalitis ..	22.4	11.0	26.3	5.3
Others ..	?	2.7	?	0
Total ..		18.4		5.3

adult life—a highly significant difference. The presumed diminution of risk to an individual vaccinated in infancy and revaccinated as an adult—which was one of the pillars on which our policy was founded—can be seen to be fallacious. It is also often said that infant

*Verbatim text of paper delivered at Symposium on Virus Diseases at the Annual Meeting of the British Medical Association, Belfast, 1962; with addenda as footnotes.

vaccination provides protection for life. This is not so. It has been calculated (Dixon, 1962) that after single-insertion primary vaccination the chance of any attack of smallpox is reduced as follows:

If vaccinated within						Chance of smallpox reduced by	
1 year	..	..	..	..	..	1:1,000	
3 years	..	..	..	..	..	1:200	
10 years	..	..	..	..	..	1:8	
20 years	..	..	..	..	..	1:2	

After 20 years infant vaccination has little or no effect in preventing infection.*

I have already said that even 70 to 75% infant vaccination will not protect the community against outbreaks of smallpox. There is, of course, no doubt that a group of individuals who have been vaccinated at some time in their lives will, as a group, experience a lower mortality than a non-vaccinated group when exposed to smallpox, but to produce a high degree of individual and herd immunity vaccination and revaccination must be done every few years.

I think the risk of vaccination is justified in certain groups of people—for example, immigration personnel, fever hospital and public health workers—and in these revaccination should be done yearly. Other doctors, nurses, and hospital personnel should be revaccinated every three years. The increased risk of doctors getting smallpox is well known and was again clearly demonstrated in the recent outbreak, where three doctors became infected of whom two unfortunately died. Another reason for vaccinating doctors and hospital personnel is that, in the past, unvaccinated members of this group have played an important part in the dissemination of smallpox.

What are we to do in the case of the general population? Encourage universal vaccination in infancy and revaccinate every five years? Such a procedure would result in fewer deaths from smallpox and less chance of spread of smallpox when the virus is imported. *But* such a policy would result in far more deaths from vaccination. What is the alternative? To keep our vaccine till the need arises and to rely on epidemiological control.

Epidemiological Control

Epidemiological control means in the first place careful port control. I think that you will agree that people coming from epidemic areas should have been vaccinated or revaccinated 14 days before arrival and should have proper vaccination certificates to this effect. Attention should be alerted, either in the *British Medical Journal* or elsewhere, to those parts of the world experiencing epidemics. But in spite of careful port control an occasional case may slip through. So, secondly, epidemiological control demands that a rapid and accurate diagnosis of the case must be made by the general practitioners with the help, if necessary, of the

* *Addendum*.—"In outbreaks of variola major in Great Britain from 1942 to 1953 inclusive there were 362 cases with 89 deaths giving a mortality rate of 24.6%. From the outbreaks of those years for which published records are available the following figures have been obtained: of 64 cases of persons unvaccinated before infection 31 died, a case mortality of 48.4%, while of 111 patients vaccinated before infection 15 died, a case mortality of 13.5%. *The deaths among the vaccinated occurred in persons who had been vaccinated more than 20 years previously, except in one patient who had been vaccinated 13 years before.* (My italics.) Similar findings were recorded in outbreaks among troops abroad" (Downie, 1961).

medical officer of health and smallpox consultant. Any diagnosed or suspect case must be immediately removed to a smallpox hospital and never, of course, to a general hospital. Fourthly, it requires the immediate tracing and selective vaccination of all known and probable contacts, and the Ministry of Health epidemiologists have shown how expertly this can be done. This method of epidemiological control would not differ if a case of smallpox were imported into a highly vaccinated community.

May I add that unless things get out of hand there is no place for the panic mass vaccination which was recently *forced* on medical officers of health in some areas, with all the unnecessary illness, complications, and deaths from vaccination. The low rate of infant vaccination was *not* the reason, as suggested by the Minister of Health (1962), why "almost the whole population of Bradford had to be vaccinated in one week during January." The recent outbreak of smallpox *didn't* prove the wisdom of a policy of infant vaccination. Medical officers of health have repeatedly demonstrated their ability to control and prevent the spread of smallpox without panic when an importation occurs.

Vaccination Policy

What vaccination policy do you wish to adopt? Certainly we must move away from the idea that there is virtually no danger from smallpox vaccination and we must be prepared to weigh up the risks. There are three possible policies. The first is to muddle on as we are doing with very incomplete vaccination and still less revaccination, with all the attendant complications and deaths. With such a policy we are simply taking risks and it gives us little or no epidemiological security. I don't think anyone could argue that this is a good policy to follow. The second policy is to try to get a high universal acceptance of infant vaccination. This would produce immune infants, partially immune children, and generally susceptible adults, and it is worth remembering that smallpox in this country is not a disease of infants and is most likely to attack and be spread by adults.

If this policy of universal infant vaccination is followed and every baby is vaccinated as the Minister of Health (1962) is apparently suggesting, then he is asking for a sacrifice of at least 20 babies a year.†

Such a policy of infant vaccination would make only about 10% of the population immune at any one time. All this for what return? Very little, for this immunization rate would not have any material effect on the spread of smallpox.

In order to obtain a highly immune population repeated revaccination of nearly everyone at least six times during life would be required. If this is what we want then we must be prepared to sacrifice at least 30 individuals a year and in addition produce about 30 neurological or psychiatric cripples who have survived their post-vaccinal encephalitis. These figures are, I think, an underestimate of the deaths and complications which are required to provide a highly immunized herd. In any event I don't think that administratively a policy of universal infant vaccination and repeated revaccination would be likely to succeed in this country. The production of a high herd immunity in Britain is, I think, not only impracticable but is undesirable.

We now have ample evidence that we can stop epidemics of smallpox from occurring in this country

with only *occasional* recourse to mass vaccination. In Britain smallpox is one of the easiest diseases to control. The efficiency of modern methods of epidemiological control was recently given a very severe test and has stood up to its greatest challenge for many years. The success of this method makes it now possible for us to consider the third policy, which is to abandon infant vaccination and depend on epidemiological control. We have sufficient evidence over the years that many more will die from smallpox vaccination than from smallpox. All the known facts about the success of epidemiological control and the deaths and sequelae from smallpox vaccination make me believe that we should now give up routine infant vaccination and depend on epidemiological control. (At the same time we must not prevent those members of Parliament who recently requested the return of compulsory vaccination from having their own infants vaccinated.) This, I believe, is the policy with least risk to the individual and the community, and is the one I think we should adopt. *But*, as Wilson (1947) said in discussing B.C.G., "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."

What I have said is in flat contradiction to the view expressed by the Minister of Health (1962) at the Royal Society of Health. He was asking you to increase infant vaccination, to spend the lives of 10 to 20 infants a year for a minimal increase in our epidemiological security. I would ask him instead to spend a little more effort on devising a plan to reduce the risk of importation of smallpox into Britain.

† *Addendum*.—This figure of 20—that is, approximately 2 deaths in each 100,000 primary infant vaccinations—is based on (a) the mortality rate of 1.5 deaths per 100,000 primary vaccinations in the 1951-8 period, (b) the belief that a proportion of post-vaccinal deaths are not recognized, and (c) on the assumption that all or nearly all babies would be vaccinated if there was a drive for universal infant vaccination. The 1951-8 figures were used because it was considered that they had been carefully evaluated by Griffith (1962) and by Dixon (1962) from Ministry of Health data. More recent data (*Sunday Times*, July 29, 1962) show that among 2,600,000 babies vaccinated during the past 10 years there have been 27 deaths, or a rate of 1.0 per 100,000. I think that there is considerable under-reporting of vaccinia complications. How often are the recognized complications (such as bacterial infection, generalized vaccinia, post-vaccinal encephalitis, *eczema vaccinatum*, and progressive vaccinia) reported? How common is fatal hyperthermia associated with vaccination (Apostolov *et al.*, 1961)? How many deaths occur from contact *eczema vaccinatum*? How often does thrombocytopenic purpura follow vaccination (Meindersma and de Vries, 1962)? How common is post-vaccinal glomerulonephritis (Koster and van Tilburg, 1953) or vaccinal osteomyelitis? How often is it remembered that in fatal post-vaccinal encephalitis the brain may show little change and that perivenous microglia encephalitis does not always occur in children under 2 years old (de Vries, 1961)? Quite apart from these deaths, how many non-fatal post-vaccinal encephalitic babies are permanently damaged? It seems that my estimate that 20 babies a year—that is, approximately 2 per 100,000 primary vaccinations—would be "sacrificed" to universal infant vaccination in this country may even be an underestimate when one adds (a) deaths not recorded because of under-reporting of recognized complications, (b) deaths from unrecognized complications, and (c) the sequelae of post-vaccinal encephalitis (although perhaps rare) to the reported mortality of 1 to 1.5 per 100,000 primary infant vaccinations.

May I say that *I am a firm believer in the efficacy of smallpox vaccination when used to protect the right people at the right time? The vast majority of people living in the United Kingdom are not at risk from smallpox, never have been at risk, and probably never will be.* If and when individuals or even communities are at risk, vaccinate them, but don't do it until the risk is clearly more than the risk of vaccination itself.

Immunization Against Poliomyelitis

Up till this year immunization against poliomyelitis was carried out with the Salk type of vaccine. This vaccine is a killed virus vaccine and achieved a great measure of success in many parts of the world.

In Figs. 1 and 2 are presented the annual number of cases of poliomyelitis in the U.S.A. and in England and Wales respectively from 1940 to 1961. The arrow indicates the time when immunization with Salk vaccine

FIG. 1.—Annual incidence of poliomyelitis in U.S.A., 1940-61.

got under way. You will see the drop in the rates of poliomyelitis after the introduction of Salk vaccine. (Similar results have been obtained in other countries with immunization programmes using Salk vaccine.)

This great reduction of poliomyelitis achieved by killed vaccine is the background on which the oral vaccine was introduced. Why was there a sudden change in policy? Was there some prejudice against the use of killed virus vaccine? Salk vaccine has been one of the safest vaccines ever used. So it was not on a question of safety that the change has been made. What about effectiveness? Used as it was in the United Kingdom the effectiveness was about 90%, and it is now known how to improve the vaccine to increase this to near 100%.

In order to be effective vaccines must be of suitable potency. For years we were prepared to put up with Salk vaccines of suboptimal potency, particularly with regard to the type 1 component, and, as is known, type 1

has been the most important of the three types of virus as a cause of clinical disease. With poliomyelitis immunization campaigns the magical 75% figure was again produced, as being the goal to be achieved, and this quite unsatisfactory and illogical rate of immunization was often achieved by having high rates of immunization among schoolchildren, who are administratively easy to immunize, and low rates among

FIG. 2.—Annual incidence of poliomyelitis in England and Wales, 1940-61.

pre-school children, who are harder to get at but who are the most important transmitters of virus in the community and who most require immunization against poliomyelitis. Many of the vaccines available in the past were of such low potency that it is unlikely that they were effective in producing immunity when given to babies under 9 months of age. It is no fault of the general practitioners that efforts were not made to immunize the right people. The importance of the pre-school child was never adequately stressed by the authorities.

We had a vaccine which was safe, which could be made more potent, and which we knew how to use effectively. Instead of improving this known, thoroughly tested, and tried product, the authorities decided to make an about-turn and go over to oral living virus vaccines. It is difficult to know what prompted this decision.

Oral polio vaccine viruses spread quite readily from person to person, and in this respect they differ from all other vaccines we have used. Since the earliest trials of oral vaccines, which in the United Kingdom were done in Belfast, it has been known that the virus excreted by a vaccinated individual—that is, the virus which may infect contacts—is altered in character. It is often of slightly increased virulence and as a result of person-to-person passage may have an enhanced ability to spread. The virus which any of you may acquire from your vaccinated children would fail to pass the neurovirulence and identification marker tests which must be adhered

to in the manufacture of the vaccine virus. This fact does not mean that the vaccine viruses acquired by contact are dangerous, but it does mean that the assessment of vaccine safety in the field is a vastly more complex problem than it is with other vaccines. The spread of vaccine viruses means that a number of the Ministry's recommendations and contraindications on the use of oral vaccine are meaningless and impossible to implement.

Russian Experience

The bulk of experience on the safety and efficacy of oral vaccines comes from the U.S.S.R. In order to reduce the chance of prolonged circulation of vaccine strains in the community and to reduce the theoretical risk of vaccine virus becoming virulent, the Russians have fed as many of the susceptible population in a given area in the shortest possible time they could. We are the first country to go over to oral vaccines for continuing routine immunization. In doing so we have created certain precedents. In the first place, we went away from the Russian method of mass immunization and we are the first country to dribble oral vaccine into the community. Secondly, in the past, oral vaccines have been given largely in the off-season for poliomyelitis. We are using them throughout the year. Until we know *why* poliomyelitis is seasonal I don't think we can feel completely happy about this. Thirdly, the dose of vaccine which we are using has never had an extensive field trial anywhere. In fact, with these precedents we are conducting a large-scale trial. But are we evaluating it properly? Have we had any guidance on what we should be keeping our eyes open for? *

We do not yet know that oral vaccine is as safe as Salk vaccine. From a theoretical and practical point of view one of the things which have worried me most about polio vaccines is the presence of contaminating viruses. Our knowledge of these is as yet incomplete, and both killed and live virus vaccines have potential dangers. It is a pity having run one gauntlet apparently unscathed we should opt to run another. We do not know if oral vaccine is as effective as Salk vaccine. We do not know when booster doses will be required.

This year the Russian plan is to re-feed the whole population under 14 with two more doses of vaccine, making a total of six to eight doses for the majority of people over a period of three years. How often is re-feeding going to be necessary in the United Kingdom?

One advantage claimed for oral vaccine is that it produces resistance of the *gut* to infection by wild viruses. Much more information is required about this, and it is not known how long it lasts. It has also been claimed that oral vaccine has a marked community protective effect, but it is seldom realized that wide coverage of the population with potent killed vaccine has a profound effect in limiting the spread of polio viruses in the community.

Time will tell whether we should have chosen this new type of vaccine even if at first sight it seemed superficially easier to administer. Some of us think that it

* *Addendum.*—It took quite a number of years before the risk of provocation poliomyelitis was appreciated. It seems (and we are all conscious of this from another field) that a complete and thorough surveillance should be continuously done and the available data of the surveillance be made readily available to all doctors.

would have been wiser to take advantage of the recent technological advances in Britain which have made the production of highly potent killed vaccines possible.

Quadruple Vaccine

Quadruple vaccine (Dane *et al.*, 1962) containing this highly potent killed polio vaccine combined with diphtheria, tetanus, and pertussis will, I believe, soon be generally available. It could be given as indicated in Table III. We are at present investigating its use in babies under 6 months of age.

TABLE III.—*Proposed Modification of Schedule Q Using Quadruple Vaccine*

Age	Visit	Vaccine
6 to 9 months	1 4 weeks interval	Quadruple
	2 4 weeks interval	"
15 to 18 months	3 4	"
	4	"

Quadruple vaccine—poliomyelitis, diphtheria, pertussis, tetanus.

This new British quadruple vaccine has advantages over the combination of oral polio vaccines and the "triple" antigen. It can greatly simplify the task of many general practitioners and medical officers of health. Consider the advantage to the mother in the simplicity of this procedure. The number of visits in the first 18 months of life is reduced to four, instead of six or seven visits with the present schedules P and Q for oral and "triple" vaccine. Greater protection is afforded against pertussis, diphtheria, tetanus, and, I believe, poliomyelitis than with other schedules of immunization. Individual protection against poliomyelitis as measured by antibody responses will be at a higher level than after oral vaccine. There would obviously also be a greater chance with this vaccine of obtaining high overall infant immunization rates against diphtheria, tetanus, and pertussis as well as poliomyelitis, and maintaining these over the years. To quote the *Lancet* (1962): "The severe localized outbreaks of diphtheria last year, and the tragic cases of tetanus and tetanus-serum reactions, emphasize the importance of this approach." When a single vaccine incorporating the four antigens is used the only question to ask the injured child's parent or the injured adult is, "Has he been immunized?"

The Minister of Health (1962) suggested that we have to get away from panic immunization; with this I fully agree. According to the press, he called for a drive to raise the standards of immunization against all infectious diseases and said that this did not mean a crash programme against any one disease but a comprehensive and planned programme of immunization and vaccination in every part of the country. Whether or not we accept what the Minister said on smallpox vaccination, all of us will whole-heartedly agree about increasing the immunization rates against poliomyelitis, diphtheria, tetanus, and pertussis. Those who have extolled the use of community campaigns with oral vaccine and have stressed that the "painful injection" was a thing of the past have probably done a great disservice to maintaining good immunization rates against diphtheria, tetanus, and pertussis—"I'll wait, Doctor, till the baby can have the other immunization by mouth." These children are still waiting.

The developmental potential of combined killed virus vaccines is great. Suitable vaccine combinations can be made with the components required for various age-

groups. It may be that as poliomyelitis disappears one or other of the Coxsackie or E.C.H.O. viruses might loom into greater prominence. It will be a relatively simple thing to add an inactivated Coxsackie or E.C.H.O. virus to the combined vaccines, but it will be very complex to develop and test another attenuated live virus for oral use.

Among the viruses which could also be added is a killed vaccine against measles devoid of all the complications associated with live measles virus vaccines. It should also be possible to add adjuvants to these combined vaccines—that is, substances which can greatly enhance the immunizing properties of the vaccines—and with adjuvants the number of injections could be further reduced.

Respiratory Viruses

Perhaps at this point I should hand over to the Chairman, and ask him what we can hope for in the control of respiratory viruses by vaccines in the next 10 years.

I personally believe that influenza vaccines should be generally available to everyone who wanted vaccine and not only to selected high-risk patients. The fairly wide use of "flu" vaccines will encourage active commercial work in this field, so that the preparation of a special vaccine in the face of an epidemic of a new dangerous "flu" virus is possible. The ability to deal with a new killer strain will depend on plant and personnel being available now for a crash vaccine production programme.

More trials must of course be done. We must not be content with a figure of 40 to 60% protection over a period of a few months, which is about the figure obtained with some recent British aqueous vaccines. I hope that the same goblin which kept the potency of Salk vaccine too low for too long is not also hovering over the "flu" vaccine field.

I doubt if there is much hope in the near future for the general introduction of useful vaccines against all colds and all other infections of the respiratory tract. After all, if we vaccinate against all of them we will never be ill and, comparatively speaking, will never know what it feels like to be well! The approach to the control of most of these other minor respiratory infections will be perhaps by new chemotherapeutic substances. None is yet really in sight.

Conclusion

In conclusion may I say that in the space age which we are entering vaccines will not be prepared by cookery, but be made from purified antigens which can be accurately measured and scientifically blended to produce a predictable response. They will contain a large number of different killed viruses with adjuvants which can enhance their effect and produce lifelong immunity. They will be administered in a single injection with a disposable individual injector, which gets rid of the syringe problem. Some of the new developments in vaccines which I have mentioned can be available if you want them and ask for them. But all vaccines have to be evaluated even if, at first sight, they seem safe and effective.

We don't need a lot of new knowledge to influence markedly the health of the community, but we do need to apply intelligently what we already know without prejudice and be prepared to change our policies on the evidence available.

At a meeting recently a friend of mine produced the following quotation from J. J. Rousseau. "Si quelquefois les savants ont moins de préjugés que les autres hommes, ils tiennent en revanche, encore plus fortement à ceux qu'ils ont." This is applicable to our vaccination policies. If I may translate "savants" as "doctors and scientists" the quotation could read: "If doctors and scientists have fewer prejudices than other men, they hold all the more strongly to the few they have."

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THIOTEPA IN TREATMENT OF ADVANCED BREAST CANCER

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The problem of how to deal with an individual case of advanced carcinoma of the breast is one that confronts every clinician working on malignant disease. We feel that such patients should always be treated initially by simple hormone administration for a trial period to determine whether they can be controlled in this way. If this is not possible they should then be considered for endocrine surgery or chemotherapy. The results of chemotherapy with thiotepa (triethylene thiophosphoramide) in a group of 46 such patients are reviewed below.

Watson and Turner (1959) reported the use of thiotepa and testosterone given concurrently in breast cancer, having obtained the remarkable objective remission rate of 85%. Seven out of 34 of their patients were stage 2 cases; but, even if these are excluded, 23 of the remaining 27 patients with metastatic disease were said to show some measure of control. Cree (1960), using the same technique, had similar results in 17 patients.

We were anxious to see if we could repeat these results and so develop the treatment as an alternative to endocrine surgery. We also hoped to find points in the patients' history and in their general pattern of disease which might guide us in assessing the chances of response.

Material and Methods of Treatment

All the patients considered for the treatment were suffering from progressive metastasizing breast cancer. All had had a trial of hormone therapy and had either responded initially and subsequently relapsed or had failed to respond. If there was clinical or biochemical evidence of liver involvement or the general condition of the patient was very poor, thiotepa therapy was withheld. All deaths occurring in less than one month from the end of treatment were regarded as being caused by the drug.

A patient classified as receiving benefit from treatment had to show evidence of objective remission on radiological, photographic, or clinical findings. Before a positive result was claimed such improvement had to be maintained for at least three months after the last dose of thiotepa had been given. Subjective remissions were not considered significant, as the large doses of testosterone produced feelings of wellbeing in almost all

the patients, even in those in whom the disease was obviously advancing. Before starting treatment relevant photographs and radiographs were taken and liver-function tests and a full blood count were performed.

The doses of thiotepa and testosterone followed closely those suggested by Watson and Turner, though in our experience it was not possible to give some of the larger quantities they used. The scheme was as follows:

1. Testosterone propionate. 100–200 mg. daily five days a week by intramuscular injection. This substance was continued until the patient's discharge from hospital.
2. Thiotepa. After the first five injections of testosterone 15 mg. of thiotepa was given by intramuscular injection. This was followed on alternate days by 30 mg. until a maximum of 285 mg. had been given. If the white-cell count fell below 2,000/c.mm. or the platelets below 100,000/c.mm. the drug was stopped.
3. Full blood counts were carried out every second day.
4. Some cases had two courses of treatment.

Results

Pattern of Treatment Response (Table I)

A total of 46 patients were initially selected for treatment, and five of these died as a result of it. This mortality of 11% was comparable to what we have experienced with hypophysectomy. Of the 41 patients who survived treatment 17 had an objective remission as judged by the criteria already given. This was 37% of the total number of patients in the series and 41% of those who survived the treatment. The mean duration of the period of control was 7.5 months and the mean survival after the disease had become reactivated was 4.5 months. It was of interest that this latter figure was almost the same as the duration of survival in those who failed to show any response.

TABLE I.—Incidence and Duration of Remissions

Number of cases in series	..	..	..	46
Treatment deaths	..	..	..	5 (11%)
Objective remissions (overall)	..	..	..	17 (37%)
Mean survival after completion of treatment (months):				
Remissions:				
Period of response	..	..	..	7.5+
Total survival	..	..	..	12.0+
Failures:				
Total survival	..	..	..	4.0+