since 1939 must be considered in relation to the change in the mortality from, and social distribution of, cancer of the larynx. Television might in time have a similar effect, owing to lessened consumption of alcohol, but the results could hardly be apparent as yet.* Cancer of the oesophagus, of which the incidence is certainly high upon occupations concerned with the consumption of alcohol, shows a similar diminution in social gradient.

Cancer of Bladder and Kidney

An increase in cancer of the bladder in recent years has occurred both in Denmark (Clemmesen and Nielsen, 1956) and in England and Wales (Registrar-General, 1954, 1955) (see annotation, this *Journal*, January 26, 1957, p. 218)

Clemmesen and Nielsen say: "... there has been a steady increase in the number of cases notified for papillomata and carcinomata of the urinary bladder among men in the capital. In provincial towns and rural areas a less pronounced increase occurred during the years 1951 to 1953, the significance of which is doubtful, so far. No increase in incidence was observed for tumours of the bladder among women nor for malignant neoplasms of the kidney."

The Registrar-General's figures, on the other hand, show an increase in both sexes in cancer of the bladder and of the kidney in the eleven years 1944-54 (Table X). The percentage increase in the death rates for cancer of the bladder is somewhat greater in women than in men, and for cancer of the kidney it is equal in the two sexes.

Possible Effects of Tobacco upon the Urinary Tract

The importance of a search for carcinogenic effects of tobacco other than those upon the mouth and respiratory tract has been emphasized in a recent paper (Kennaway, 1955) in which attention is drawn to the antidiuretic action (Walker, 1949) which must facilitate any such carcinogenic effect. The quantity of compounds absorbed from tobacco smoke is made plain by the very numerous investigations of their effects upon the circulatory system (see, for instance, Wynder, 1955, Chapters 2 and 3).

Steele, Koch, and Steiner (1951) obtained fibrosarcoma in about 19% of mice after subcutaneous injection of an extract (butyl alcohol, after extraction with benzene) of human urine, presumably from unselected persons. Dr. A. J. Lindsey allows me to say that he is examining, at the Sir John Cass College, the urine of smokers and of non-smokers for compounds which he and his fellow-workers (Commins *et al.*, 1954; Cooper and Lindsey, 1955) and J. A. Campbell in this laboratory have identified in cigarette smoke.

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*The number of television licences in England and Wales rose from 18,730 in May, 1947, to 2,957,000 at the end of 1954.

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BENACTYZINE AS AN AID IN TREATMENT OF ANXIETY STATES

PRELIMINARY REPORT

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Benactyzine hydrochloride has been found to reduce or modify stress-induced behaviour in animals (Jacobsen and Sonne, 1955; Jacobsen and Skaarup, 1955a, 1955b). It has also been found to diminish the autonomic responses of human beings to emotionally disturbing experiences (Jacobsen *et al.*, 1955). Favourable results have been reported in Denmark with clinical use of the drug for the treatment of psychiatric cases (Jensen, 1955; Ostenfeld, 1955), and it has recently been introduced into the United Kingdom. Beresford Davies (1956) reports its use in a group of 110 patients suffering from psychiatric conditions, with favourable results in 67 patients. Further trials have been reported by Raymond and Lucas (1956) and Seager and Leitch (1956).

In recent years a variety of new drugs—the so-called "tranquillizers"—have been introduced in psychiatric practice, some of which are now being prescribed very extensively—so extensively, in fact, that the American Psychiatric Association has issued a warning against their indiscriminate use, and hospital management committees in this country have expressed concern at the high cost incurred by their use in mental hospitals. For some of these drugs the value in specific conditions has been thoroughly assessed—for instance, in the case of reserpine or chlorpromazine employed for the treatment of chronic disturbed hospitalized schizophrenics. But the widespread use of drugs of this type for the treatment of psychoneuroses in general practice rests on no such secure evidence.

If the preliminary findings of the clinical use of benactyzine prove valid it appears likely that its application may lie mainly in the treatment of certain types of psychoneurotic patients, in which case its chief use would be found in general practice and in psychiatric out-patient clinics. It seems therefore to be of particular

importance that its value in such a type of practice should be rigorously assessed as soon as possible.

None of the clinical papers previously quoted can be regarded as entirely conclusive as an assessment of the value of the drug from the point of view we have in mind. Jensen's series of 110 cases consisted predominantly of in-patients in the Danish Red Cross Sanatorium, since it included only 14 out-patients. From a diagnostic point of view the series is heterogeneous, as it contains many different types of psychoneurotic and some psychotic reactions. Beresford Davies's series also contains patients suffering from many different types of psychoneurotic and psychotic reactions. Of his 110 cases 74 were out-patients, the remainder being in-patients in a mental hospital, some of whom were receiving modified electroplexy at the same time and others drugs of the antihistamine group. (It is not clear whether chlorpromazine was included in this category.) The 13 in-patients studied by Seager and Leitch are diagnostically an extremely heterogeneous group, since they include no fewer than four different types of psychoneurotic syndrome, and the only results presented are those for the group as a whole. Raymond and Lucas, on the other hand, although their series of 43 out-patients contains five different diagnostic groups, present the results for each group separately, from which they conclude that benactyzine had a favourable effect on 12 out of 18 cases of "anxiety neurosis."

Jensen's series includes a "control" group which is said to have been "picked out at random but so that approximately the same types of patients are represented in both groups." It seems to us that there may be a certain incompatibility between the first and second statements in this sentence. It is open to the further objection that the patients in the control group were apparently receiving three different treatments—thiopentone or phenobarbitone, "the latter often combined with bromides"—and that the psychiatrists undertaking the assessments were aware of the treatments which the patients were receiving, except that, at a later stage of the trial, in the case of 40 patients who had responded well to benactyzine, placebo tablets were substituted unknown to the patients' nurses and the colleagues of the author but apparently with the knowledge of the author himself. In Beresford Davies's series no control group was employed, and Ostenfeld's material consists of nine diagnostically heterogeneous case reports without controls. The trials reported by Raymond and Lucas and by Seager and Leitch were both blind and also controlled in the sense that the patients were used as their own controls by the blind alternation of placebo and drug. Unless combined with independent controls this method has, however, the disadvantage of providing no information on the course of the malady in comparable patients who do not receive the drug being investigated.

The method of assessment of the patient's condition is not fully described in any of the papers, except that of Raymond and Lucas (1956). In Jensen's series three general categories—"good effect," "moderate effect," and "no effect"—are employed; Beresford Davies similarly uses two sets of three categories—"worse," "unchanged," and "improved," and elsewhere in his paper "fair," "good," and "marked" improvement. In both these series it appears that different psychiatrists made assessments on different cases. No attempt is made to categorize the degree of improvement shown by Ostenfeld's cases.

In planning our own trial it appeared to us important to eliminate as many as possible of the uncontrolled variables which we have outlined above, or, where they could not be eliminated, to measure the significance of their effect.

Design of Trial

We decided to accept for the trial out-patients between the ages of 20 and 65 suffering from an anxiety state of less than four years' duration. We excluded any patient whose condition merited immediate treatment as an in-patient by reason of the severity of the anxiety, or patients in whom marked depressive symptoms appeared at the outset to be the principal feature. Three psychiatrists participated in the trial. Each patient was seen weekly for at least eight weeks by the psychiatrist who conducted the initial consultation. At the end of the second and fifth weeks—that is, at the third and sixth interviews—a second psychiatrist also saw the patient. Four treatments—A, B, C, and D—were available for prescription. Each psychiatrist was provided with a different list of these treatments arranged in random order, and the treatment prescribed for each new patient taken into the series by a psychiatrist was dictated by the next treatment on his random list.

The three possible combinations of psychiatrists to undertake the double interviews at the end of the second and fifth weeks were allotted in the same way. For any individual patient the third and sixth interviews were conducted by the same pair of psychiatrists. The chief pharmacist at the hospital, without our knowledge, allotted two of the treatments A, B, C, and D to benactyzine tablets, 1 mg., and the other two to placebo tablets of identical appearance.

At the first interview the psychiatrist prescribed for the patient the next treatment code letter on his random list at a dosage of one tablet three times a day. During the first fortnight—the preliminary period—all patients received inert tablets. In this period the fact that the tablets were inert was known to the psychiatrist but not the patient. At the third interview the dosage of the prescription was changed so that during the succeeding week it rose by one tablet a day to a maximum dose of two tablets four times a day. From this interview onwards the pharmacist dispensed tablets according to his code, and it was not known to the psychiatrist or to the patient whether the latter was receiving inert or active tablets. Unless side-effects led the psychiatrist to decrease the dose, the patient continued to receive the tablets at the rate of two tablets four times a day until the sixth interview. At this time all tablets were discontinued for one week. At the end of this week the patient was then placed on "known" benactyzine prescribed by name and continued as an ordinary out-patient at the clinic.

In summary, therefore, the trial provides a preliminary period of two weeks in which the patient is known to be on inert tablets, a test period of three weeks during which it is known only to the pharmacist whether the patient is receiving benactyzine at a dose starting with 1 mg. three times a day rising within five days to 2 mg. four times a day, and remaining at that level until the end of the test period, or, alternatively, is receiving the same dosage of inert tablets. This is followed by a withdrawal period of one week, after which the patient is given "known" benactyzine for at least two more weeks.

The first interview, which lasted about one hour, was devoted to a full psychiatric examination. At the end of this interview an assessment of the patient's symptoms was made in a manner described below. Succeeding interviews varied in length up to three-quarters of an hour. These interviews were devoted to minor psychotherapy and to an assessment of the extent of the patient's symptoms during the preceding week. At the third and sixth interviews a second psychiatrist was present—the external examiner—who made an independent assessment of the patient's symptoms.

The psychiatrist in charge of the case was at liberty to prescribe a nocturnal sedative during the trial if the severity of the patient's sleep disturbance made it imperative. In only one case was this found to be necessary. No drugs other than those under trial were prescribed by day. The psychiatrist was at liberty to reduce the dosage of the drug under trial if side-effects appeared.

Assessment of Symptoms

The method of assessment of the severity of the patient's condition was given considerable attention. The usual method whereby the psychiatrist makes an intuitive global assessment of the patient's improvement under such headings as "fair," "good," or "marked" seemed open to the objection that it is difficult with such assessments to compare with any degree of accuracy the improvement of the same or different patients—in addition, such judgments provide no qualitative information on the nature of the changes in symptoms which might throw light on such matters as general prognostic differences between anxiety states of varying symptomatology or on the type of symptom particularly likely to be relieved by the drug under study. We therefore classified all the symptoms likely to be found in our patients under the following headings: (1) anxious mood; (2) tension; (3) specific fears and phobias; (4) sleep disturbance; (5) intellectual disturbance; (6) depressive features; (7) somatic disturbances (muscular and sensory); (8) cardiovascular disturbance; (9) respiratory disturbances; (10) gastro-intestinal disturbances; (11) genito-urinary disturbances; (12) autonomic disturbances; and (13) manifestations of anxiety in the behaviour at the interview.

A gloss was prepared listing the features to be taken into account in making an assessment under any of these headings. At the interview we rated each of these thirteen items on a five-point scale as follows: 0, none; 1, mild; 2, moderate; 3, severe; 4, grossly disabling.

This rating scale yields a variety of different types of information for each patient, including a "profile" of his symptomatology and, by summing the ratings for all headings, a gross symptom score.

Such in outline is the design of the trial, which provides the means for an intensive study of a small diagnostically homogeneous group of cases to elicit data relevant to many questions. This paper deals with one of those questions—namely, the comparison over a test period of three weeks of two groups of patients suffering from anxiety states, both of which received minor psychotherapy and pills: only in the case of one group, however, were the pills active.

Other matters, such as the extent of agreement between the ratings of different psychiatrists (which proved to be great, $r=0.89$), the prognostic significance of different symptom-patterns, the response of different symptoms to the drug, and the effect of changes in his life situation on the patient's illness, will be dealt with elsewhere.

Nevertheless a word must be said regarding the effect of change in the patient's life situation. While we were still unaware of the coding employed for the tablets, we identified six cases in which it appeared to us that such a factor had been operative and rejected them from the series. In five cases there was considerable improvement (an average of 13 points improvement on the patient's symptom-score during the trial period), which appeared to us to result from very favourable changes in the patient's life situation. In a sixth case a worsening of the patient's life situation appeared to us to be associated with a slight worsening of his condition (two points on his total symptom-score). When the code was broken it was found that the five patients who had improved in this way had all been receiving inert tablets, while the patient whose condition had deteriorated had been receiving benactyzine. It is evident from this that if such factors are not taken into account they may considerably bias the results of drug trials with psychoneurotic patients. In the remainder of our cases, 26 in all, there were, so far as we could tell, no changes

in circumstances during treatment to which any change in condition could be attributed.

To emphasize what we have said regarding the restricted value of global assessments of the patient's condition, such as the term "improved," we show in columns 2 and 3 of Table I our results using the categories "improved" (mean-

TABLE I

	Our Series		Davies (1956)
	Inert	Benactyzine	Benactyzine
Improved	9	14	15
Not improved	1	0	7
Worse	2	0	0
	12	14	22

ing a reduction in total symptom score between the first and second double interviews), "not improved," and "worse." In column 4 we show the results of the 22 cases of "anxious neurosis" treated with benactyzine in the uncontrolled trial reported by Beresford Davies (1956). These data show that, even after the rejection from our series of patients in whom improvement appeared to result from a favourable change in their life situation, three-quarters of the patients receiving inert tablets "improved"—as high a proportion as is attributed to benactyzine in column 4. Although the class frequencies in this table are too small to permit the use of statistical tests, the figures nevertheless make it appear unlikely that valid conclusions can be drawn regarding "improvement" in the treated groups unless the degree of improvement can be assessed in some way.

The improvement of our patients who received inert tablets may be attributed to the benefits of minor psychotherapy or the natural history of the malady, according to the taste of the reader; but, whatever its cause, such an outcome makes it evident that a drug trial in this condition is valueless unless it is controlled, unless the effect of change in the patient's life situation is excluded, and unless it attempts by some means to measure the degree, scope, and nature of the symptomatic improvement. The total symptom-score improvement, as assessed by two psychiatrists on the thirteen-items rating scale, provided us with such a means, although the raw symptom-score might be open to the objection that it does not differentiate between an improvement in a patient displaying one symptom and a more widespread but more modest improvement affecting different symptoms. We have therefore used, in addition, an index of improvement based on the percentage improvement on the patient's original symptom-score as assessed by the two psychiatrists.

Table II shows the data obtained in this way. Columns 1 and 2 show the initial and final symptom-scores during the test period of the patients who received inert tablets, and columns 5 and 6 give similar information for the "benactyzine

TABLE II

Control				Benactyzine			
(1) Initial Score	(2) Final Score	(3) Improvement Score	(4) Improvement %	(5) Initial Score	(6) Final Score	(7) Improvement Score	(8) Improvement %
22	8	14	64	28	7	21	75
27	15	12	44	14	4	10	71
37	22	15	41	8	3	5	63
39	25	14	36	23	12	11	48
28	21	7	25	44	25	19	43
34	26	8	24	32	20	12	38
13	11	2	15	31	20	11	36
46	41	5	11	23	15	8	35
22	20	2	9	42	28	14	33
32	32	0	0	34	27	7	21
31	34	-3	-10	61	49	12	20
48	56	-8	-17	20	16	4	20
				41	34	7	17
				38	36	2	5
Mean 31.6	25.9	5.6	20.2	31.4	21.1	10.2	37.5

For difference in means of improvement score, $t=1.77$ ($N=24$) $\therefore P=0.08$.
 " " " " " % improvement, $t=1.98$ ($N=24$) $\therefore P=0.06$.

cases." Columns 3 and 7 give the net improvement for "control" and "benactyzine" patients as shown by the difference between the initial and final scores. Columns 4 and 8 show the improvement as a percentage of the symptom-score at the beginning of the test period. From this table it will be seen that the average degree of improvement of the patients who received benactyzine was greater than in the case of those who received inert tablets and that this difference can reasonably be attributed to the effect of the drug.

Effect of the Drug

The effect of benactyzine in those cases in which it is evident is to produce a feeling of calmness, and sometimes a sense of detachment from such symptoms as remain, in that it diminishes rumination and preoccupation. It is our impression that it makes some patients more accessible to psychotherapy. In some cases it also appeared to have a favourable effect on sleep disturbance without the administration of any nocturnal sedatives. Patients responding to benactyzine show an improvement within a few days of its administration and, in most cases, a deterioration within a few days of its withdrawal after the comparatively short period of three weeks' medication on which the trial was based.

We found no toxic effects during the period under review, but 8 out of 14 patients receiving the drug, and 1 out of 12 of those on the placebo, showed side-effects of the type reported previously (Jensen, 1955; Beresford Davies, 1956). They complained of dizziness and "muddled thinking" amounting in a few cases to thought-blocking. In most cases these symptoms were very mild; they appeared within 24 hours of the dosage reaching 8 mg. daily and disappeared equally rapidly when the dosage was reduced. Reduction of the dosage to 6 mg. daily was sufficient to abolish the side-effects in all cases except two, in which it was reduced to 4 mg. daily.

During the progress of the trial we were inclined to suspect that an increase in depression might also be a side-effect of the drug. This suspicion was aroused by the fact that, although we had excluded at the outset patients in whom marked depressive symptoms were the predominant feature, we noticed a tendency for our ratings of depression in certain patients to increase during our observation of them.

The data derived from the trial enable the validity of this clinical impression to be examined. The mean depression-scores of the "inert" and "benactyzine" groups at the initial interview were 2.7 and 2.6 respectively. At the end of the preliminary period, during which both groups received inert tablets, the respective mean scores were 2.2 and 2.4. At the end of the trial period both groups had the same mean score of 1.8.

It is evident, therefore, that there was a general tendency for the depression score to fall to the same degree regardless of whether inert or benactyzine tablets were received. There were five patients whose course ran counter to this general tendency in that at some period of the trial their depression-score increased. Three showed such an increase only during the preliminary period while receiving inert tablets. A fourth patient showed an increase only during the trial period while receiving inert tablets, and a fifth showed an increase during the preliminary period on inert tablets and a further increase in the trial period on benactyzine.

Our suspicion that an increase in depression might be a side-effect of benactyzine therefore proves to be without support. The average fall in the depression-scores of those who received this drug is as great as in those who did not. In only one patient receiving benactyzine did an increase in depression-scores occur, and this tendency had already become manifest, before he received the active drug, by a rise in depression-score during the preliminary period.

The increase in the depression-scores may indicate a real and spontaneous increase in the severity of depressive

symptoms, or, alternatively, it may indicate the inaccuracy of assessments of depression made at a single initial interview—an inaccuracy which may diminish with assessments repeated at weekly intervals. It may well be that in some cases the depressive symptoms became more severe, but that in others depressive features became more evident to the observer as anxiety symptoms diminished. We hope to deal with this matter more fully in another communication.

Conclusions

The majority of our "placebo" patients have improved; some, we suspect, by reason of a favourable change in their circumstances, and others, we hope, by reason of the assistance which minor psychotherapy could give to their natural capacity for recovery. Several of our patients showed an increase in depression which proved to be unrelated to benactyzine.

Had our trial not been "blind" and "controlled" we should inevitably have attributed to benactyzine both favourable and unfavourable effects which, it is evident from our data, *are not* attributable to it; and had we not attempted to assess improvement in both a quantitative and a qualitative manner we should have failed to discern the favourable effects which *are* attributable to it. This trial has convinced us, firstly, of the misleading findings that may result from uncontrolled drug trials on psychoneurotic patients; we shall in future view with increased scepticism conclusions drawn from such trials. Secondly, we have learnt that, although blind controlled trials are essential, they are exceedingly time-consuming, not only because of the amount of time that must be devoted weekly to the assessment of each patient's condition, but also because a considerable proportion of the patients seen for an initial consultation with a view to inclusion in the trial failed on examination to meet the criteria we had laid down for acceptance. Even when they did meet the criteria there was another source of wastage—namely, their inability (by reason of geography or their employment situation) to attend the clinic weekly for at least eight weeks during working hours. Thirdly, we have learnt that impressionistic global judgments of a patient's condition alone are of little value in assessing the effect upon him of a particular regime, and in attempting to devise a method of symptom appraisal in anxiety states we have been disappointed to obtain little help from past literature with the notable exception of a paper by Cameron (1944). Fourthly, we have been reassured to discover that, with respect to assessment of anxiety states made in the manner we have described, doctors do not differ significantly, at least so far as we three are concerned. And, finally, we have found that, on the average, patients who received benactyzine in this trial showed a greater degree of improvement than those who did not.

Summary

Thirty-two out-patients suffering from anxiety states have received either benactyzine or an inert substance in a double blind controlled trial.

The majority showed "improvement." Six cases in which a change in symptoms appeared to us to result from a change in the patient's circumstances were discarded from the series.

Among the remaining 26 patients the extent of the average degree of improvement as assessed by two independent psychiatrists using a rating scale was greater in the case of the group of patients that received benactyzine than in the control group ($P=0.08-0.06$).

More than half the patients receiving benactyzine, 8 mg. a day, complained of side-effects, usually of mild degree, which disappeared when the dose was reduced.

An increase in depression occurring in five patients was not due to benactyzine.

Double blind controlled trials and improved methods of assessment of the patient's condition are very time-consuming; they are nevertheless essential in studying the effects of drugs on psychiatric patients in order to circumvent the capacity for unwitting self-deception which both psychiatrists and their patients display.

We thank Mr. N. W. Blacow, chief pharmacist of the General Infirmary at Leeds, for supervising the coding and dispensing of the substances under trial; and Glaxo Laboratories Ltd. for the gift of "suavitil" brand benactyzine and the matched inert tablets used in the trial.

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ANTILIPAEMIC AGENT WITHOUT ANTICOAGULANT ACTION

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There is now ample evidence that heparin influences the transport or metabolism of fats in man. When injected after a fatty meal it accelerates the disappearance of visible lipaemia (Anderson and Fawcett, 1950; Oliver and Boyd, 1953). Following heparin administration, analysis of serum lipoproteins by the ultracentrifuge shows a redistribution of the low-density fractions with reduction of the Sf 12-20 and increase of the Sf 6-12 group (Graham *et al.*, 1951). In 1953 Nikkilä reported comparable changes in the electrophoretic pattern of serum lipids after heparin, with diminution of the beta- and increase of the alpha-lipoproteins. However, this quantitative change in the electrophoretic pattern has not been found by all observers. The most constant change is an increase in mobility of both beta- and alpha-lipoproteins with an absolute decrease of the neutral fats and apparent diminution of the beta-lipoprotein (Herbst *et al.*, 1955; Kuo *et al.*, 1955; Besterman, 1957).

Thus heparin tends to rectify the abnormal lipaemia and Sf distribution associated with atheroma. There is as yet no convincing proof that human atherosclerosis will regress with heparin therapy, and to obtain such evidence a prolonged course of treatment would be required. Daily intravenous injection is impracticable, and the anticoagulant action of heparin makes repeated subcutaneous or intramuscular therapy hazardous.

To overcome this difficulty a substance is required which retains the antilipaemic properties of heparin but has no anticoagulant action. Constantinides *et al.* (1954) reported that certain sulphated polysaccharides with negligible anticoagulant action would clear turbid serum in rats, thereby establishing that the antilipaemic and anticoagulant effects were independent properties. Subsequently at the Institute of Seaweed Research Black and

Dewar (1954) showed that laminarin, a relatively homogeneous polysaccharide from the seaweed *Laminaria cloustoni*, could be sulphated to varying degrees. The highly sulphated compounds have an anticoagulant action, whereas the laminarins with few sulphate groups have little or no effect on blood-clotting. The object of the present study was to determine whether either of two lower-sulphated polysaccharides exhibited antilipaemic properties similar to those of heparin as judged by their effect on the electrophoretic pattern of the serum lipoproteins.

Method

The preparations used in this study were two samples of laminarin sulphate, M and N, with a low sulphate content—namely, 0.62 and 0.37 sulphate groups per glucose unit respectively. The anticoagulant activities of these preparations as tested *in vitro* were 1.4 and less than 1.3 international units per mg. respectively. Previous work had shown that laminarin sulphate M and N had very low acute toxicities in mice and guinea-pigs, in contrast to laminarin sulphate K, a preparation with high sulphate content which has been shown to be very toxic to guinea-pigs (Adams and Thorpe, 1957). Toxicity data are shown in the Table.

Acute Intravenous Toxicities of Laminarin Sulphates to Mice and Guinea-pigs

Animal	Substance	I.V. Dose (mg./kg.)	Deaths
Mice	Laminarin sulphate K	1,000	6/10
	" " "	1,500	9/10
	" " M	4,000	2/12
	" " N	2,800	1/9
	" " "	3,600	1/5
	" " "	4,000	5/8
Guinea-pigs	Heparin (100 I.U./mg.)	1,500	2/10
	" " "	2,500	5/5
	" " "	20	8/11
	Laminarin sulphate K	40	3/5
	" " M	200	0/5
	" " N	200	0/5
	Heparin (100 I.U./mg.)	250	0/5

These compounds, comparable to heparin in their low acute toxicity, were considered to be suitable for short-term clinical investigations.

Twelve patients with ischaemic heart disease were given an intravenous injection of 10,000 units of heparin and in 11 the electrophoretic pattern of the serum lipids was significantly altered. Only these 11 patients were subjected to further study. Nine of these patients subsequently received a single intravenous injection of 100 mg. of laminarin sulphate; six were given laminarin sulphate M and three laminarin sulphate N. The remaining two patients were given 100 mg. of laminarin sulphate M by intramuscular injection.

Samples of venous blood were taken from each patient before and at varying times from 10 minutes to 24 hours after injection. Paper electrophoresis of the serum was carried out as described by Dangerfield and Smith (1955). Each strip of filter-paper was divided longitudinally, half being stained for proteins with "light green" and half for lipids with "Sudan black B."

Two of the patients who received laminarin sulphate M had been given a fatty meal four hours before the intravenous injection. The visible turbidity of the serum and the electrophoretic pattern of the lipids were observed. To determine whether laminarin sulphate M or N altered the turbidity or electrophoretic pattern of the serum *in vitro*, 1 ml. of lipaemic serum was incubated at 37° C for one hour with 1 mg. of each of the polysaccharides.

The clotting-time of whole blood was estimated by the method of Lee and White before and after injection in five patients who received laminarin sulphate M and in two who received laminarin sulphate N.