thirds of the cases occur in the age group 11-15 and a quarter in children aged 7-11, while the infection is rare in infant departments. When more detailed inquiry is made into the age distribution of cases attending foot clinics, as Dr. A. W. Forrest has done at Leyton (personal communication), it appears that the incidence rises to a peak in the 12-13 age group and thereafter falls sharply. Although there is evidence that the wart is a self-limited infection, this maximum incidence around puberty suggests that there may be a hormonal factor concerned in its pathogenesis.

The predominance of plantar warts among girls and the increasing incidence with school age has found various explanations—the more frequent attendance at the swimming-bath, increasing use of barefoot physical training and dancing, and the use of communal plimsolls. While contaminated floors and shoes are likely vehicles for the spread of what is undoubtedly an infectious disease, they do not seem to me to explain satisfactorily the peculiar age and sex distribution. There is need here for an inquiry into possible predisposing physiological factors and for more careful observation of the habits of schoolchildren and their relationship to the occurrence of what is a readily recognizable infection. Unfortunately, the wart virus has not yet been grown artificially, so that its distribution outside the body cannot be determined. Sometimes, however, the mode of spread of an infection can be demonstrated by blocking one or other of the possible channels, and some concerted study in this direction would probably lead to more knowledge about the spread and to more rational measures for the control of plantar warts.

Conclusion

I will conclude by reminding you that infections of the skin are still a major cause of absenteeism from school and from work. In a recent survey among schoolchildren skin diseases were responsible for an absence rate of 23 per 100 children, which was greater than the absence rate from any one of the specific fevers (D. D. Reid, personal communication). I have remarked on only a few of the common skin infections—we might have discussed scabies or acne, boils, wound infections or erysipelas, or some of the ill-defined conditions whose aetiology is still obscure. I hope the dermatologists and mycologists and medical officers of health will forgive a microbiologist for wandering into their fields, but I think they will agree with me that there are still some fascinating problems to be tackled. I am convinced that problems of this kind can be tackled and solved satisfactorily only by co-operative efforts between the clinician, the administrator, and the laboratory worker.

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TRIETHYLENE MELAMINE IN HUMAN MALIGNANT DISEASE

RESULTS WITH ORAL ADMINISTRATION OF ENTERIC-COATED TABLETS

BY

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Since 1950 reports have been published on the use of triethylene melamine (T.E.M.) as an alternative to nitrogen mustard in the palliative treatment of Hodgkin's disease, of the chronic leukaemias, and of various other neoplasms of the reticulo-endothelial system. The drug has been known as trisethyleneimino-s-triazine or 9500 in this country and as triethylene melamine or T.E.M. in the U.S.A.

In our first experiments with this compound it was shown to be a potent inhibitor of the growth of the Walker tumour in rats when given in aqueous solution by the intraperitoneal or intravenous route. When given by mouth, about 50 times the parenteral dose was needed to produce a comparable effect (Rose *et al.*, 1950). These results aroused our interest in the potentialities of the compound as an agent for the treatment of human malignant disease, and, with the possibility of clinical trial in mind, its pharmacology and toxicology were studied in animals of various species (Hendry *et al.*, 1951). In the course of these studies it was shown to produce a consistent temporary fall in the peripheral leucocyte count of the dog when given intravenously in appropriate dosage. On the other hand, when it was given to dogs by mouth—in gelatin capsules containing the dry crystalline product—the effect was very variable. Because of this it was decided to adopt the intravenous route in our first clinical trials of the drug, the results of which have already been reported (Paterson and Boland, 1951). Oral dosing, however, is simple and convenient, and the possibility of employing this route with T.E.M. was kept in mind.

While our early trials were still in progress we learned that this mode of administration had, in fact, been used in clinical trials in America (Karnofsky *et al.*, 1951), where the activity of the compound had been independently discovered (Lewis and Crossley, 1950; Burchenal *et al.*, 1950). It is clear from these reports, whether experimental or clinical, that a greater variation occurs in the response to the drug when orally administered than when given intravenously. Since T.E.M. is unstable to acids it seemed likely that the erratic response to oral dosing noted in the dog was due to variable inactivation of the drug in the stomach, and that this might also account in part for the variable response in man. The possibility of obtaining a more uniform response from enteric-coated tablets was therefore explored by comparing the effect of plain and enteric-coated tablets of T.E.M. given by mouth upon the peripheral leucocyte

count in dogs. The tablets used for this and for the subsequent clinical trials were supplied by the pharmaceutical research and service laboratory of Imperial Chemical Industries Ltd. They were available in strengths of 1 and 5 mg.

Animal Experiments

Four male and two female animals were used in the main experiment. Food was withheld for one day and the compound given in a single oral dose the following morning. Water was freely available to the animals at all times; they were fed in the usual way on the afternoon of the day of dosing. One dog was given plain tablets only, two were given enteric-coated tablets only, while the remaining three received, on separate occasions, both plain and enteric-coated tablets. Dosing was on a body weight basis. A total leucocyte count was carried out at one-day or two-day intervals on blood drawn from an ear vein. After each dose the animals' white blood counts were allowed to return to normal before the next dose was given. The results of these experiments are shown in Tables I and II.

TABLE I.—Effects of Oral T.E.M. in Dogs

Dog	Dose Total (mg.)	mg./kg. (approx.)	Leucocyte Count per c.mm.	
			Initial	Minimum Recorded and Remarks
<i>Plain Tablets (and dry compound in gelatin capsules)</i>				
379	100	10½	23,100	8,470 at 17 days
380	100	12½ gelatin capsule	27,830	Dead overnight after being dosed
439	35	5.0	24,200	9,020 on day 8
439	6	0.5	24,750	No significant change
440	35	5.0	14,025	3,960 on day 3. Dog died on day 4 with negligible count
442	40	4.0	16,610	5,995 followed by prolonged low count
442	20	2.0	19,500	11,440 on day 10
454	6	0.5	19,140	440 on day 10. Dog died on day 11 with negligible count
<i>Enteric-coated Tablets</i>				
443	15	2.5	18,590	ca. 55 on day 3. Dog died on same day
442	15	2.0	13,970	1,815 on day 6
442	5	0.5	14,190	3,410 " " 9
455	5	0.6	19,580	11,165 " " 4
454	5	0.6	18,535	2,200 " " 8
439	5	0.5	24,420	4,235 " " 7
439	5	0.5	29,700	2,057 " " 8

TABLE II.—Comparison of Plain and Enteric-coated Tablets in Same Dogs

Dog	Type of Tablet	Dose mg./kg.	Leucocyte Count per c.mm.	
			Initial	Minimum Recorded and Remarks
454	Enteric	0.5	18,535	5,225 on day 4
	Plain	0.5	19,140	440 on day 10. Dog died on day 11
439	Plain	5.0	24,200	9,020 on day 8
	Enteric	0.5	24,420	4,235 " " 7
	Plain	0.5	24,750	No significant change
	Enteric	0.5	29,700	2,057 on day 8
442	Enteric	2.0	13,970	1,815 " " 6
	"	0.5	14,190	3,410 " " 9
	Plain	2.0	19,500	11,440 " " 10
	"	4.0	16,610	5,995 on day 2, followed by prolonged low count

It will be seen from these tables that with plain tablets or gelatin capsules the effect produced by the drug bears little relation to the dose. For example, dog 379 survived a dose of 10 mg./kg. and dog 439 a dose of 5 mg./kg., whereas dogs 440 and 454 died with doses of 5 and 0.5 mg./kg. respectively. It is possible that dog 454, which had had a previous treatment with enteric-coated tablets, may have died of a cumulative effect in spite of apparent recovery of the white-cell count.

The response to the drug in enteric-coated tablets is much more consistent. A single dose of 2.5 mg./kg. in this form proved fatal, but a dose of about 0.5 mg./kg. regularly produced leucopenia without a fatal issue.

Clinical Trials

A total of 44 patients have been treated, and this report concerns all except one patient who was moribund on admission and died the day after his treatment. The cases were advanced, most of them being untreatable by radiation, or having ceased to respond to radiation, to urethane, to nitrogen mustard, and to intravenous T.E.M.

Preliminary haematological investigations were always done, and in addition the standard tests to determine hepatic and renal sufficiency. Acute renal failure has not been recognized after the use of T.E.M., and where renal damage has been discovered by post-mortem examination the findings have been consistent with the primary disease, and in one case were explicable as a late effect of localized x-irradiation.

No dietetic restrictions were imposed on the patients at the time of administration of the drug.

Hodgkin's Disease

Twenty-two cases were treated with oral T.E.M. In each case the diagnosis was verified histologically. The effects in those cases are briefly summarized in Table III. In most instances about 0.3 mg./kg. was administered as a single dose. Most of the patients so treated complained of slight and transient nausea; in five vomiting occurred and in two diarrhoea. Patients who were given the drug over a longer period had no gastro-intestinal symptoms.

In over two-thirds of the 22 cases a satisfactory remission of symptoms has been seen. The general condition of the patient improved in all but five instances.

The effect on fever was studied in seven patients who had an elevated temperature on admission. Of these, six became afebrile and in one the fever was uninfluenced (Case 20). One patient who was initially afebrile developed fever after treatment, coincident with the development of a pleural effusion.

Enlarged lymph nodes decreased in size in most cases; decrease in the size of the spleen was more varied and occurred chiefly where the spleen was not greatly enlarged.

Skin itching subsided in most of the patients with this symptom, but in some of them the relief lasted for only one or two weeks.

Pleural effusions have shown little diminution in our cases; in one the effusion almost disappeared (Case 20); in two others the effusion required aspiration on many occasions and afforded an opportunity to find whether the drug injected intrapleurally at the time of aspiration would be effective in countering the pleural extension of the disease. The small experience did not lead us to regard this as a worth-while measure.

It is almost impossible to gain an accurate assessment of pain. However, in all patients admitted with pain, whether spinal, pleuritic, or abdominal, relief was reported; this was most convincing in the five patients suffering from the pain of spinal deposits.

Cases 3, 8, and 10 showed a steady rise in haemoglobin of over 2 g. per 100 ml. In the majority the haemoglobin level remained about the same. Case 9 showed a significant fall in the haemoglobin level 52 days after treatment, but by the 67th day the original level had been regained.

The total improvement in the patient and his symptoms has been of rather limited duration. Remissions of eight to twenty weeks have been regarded as worth while. Subsequent treatments in the same patients have generally yielded less satisfactory results. On the whole the effects on Hodgkin's disease of T.E.M. given orally are similar to those obtained by intravenous injection and closely resemble those of the nitrogen mustards. The side-effects on the haemopoietic system are also similar. Leucopenia, which has been defined as a fall in the total white count below 4,000 per c.mm., occurred in 13 out of the 22 cases. In six of these patients the leucopenia was serious; thrombo-

TABLE III.—*Hodgkin's Disease Treated with Oral T.E.M.*

Case No.	Sex and Age	Total Dose mg./kg.	Overall Time of Administration	Effect on Disease				Other Manifestations	Duration of Benefit (Weeks)	Remarks
				General Condition	Nodes	Spleen	Itching			
1	M 56	0.3	1 day	Improved	Decreased	Decreased	Decreased	Fever and mediastinal nodes decreased	12	Leucopenia
2	M 25	0.3	1 "	"	"	—	—	Fever and abdominal pain decreased	7	
3	M 67	0.3	1 "	"	"	—	—	Dyspnoea decreased	22 still well	Severe leucopenia
4	F 25	0.3	1 "	"	"	Decreased	—	—	8 "	Leucopenia
5	F 23	0.3	1 "	"	"	—	—	—	9 "	"
6	F 32	0.28	1 "	"	"	—	—	—	8 "	"
7	M 56	0.3	1 "	Remained good	"	Decreased	—	—	23 "	"
8	F 30	0.3	1 "	Improved	"	—	Decreased	Abdominal mass unchanged	22 "	3 doses within 6 weeks
9	M 63	0.2	1 "	"	Unchanged	—	Unchanged	" "	" "	"
10	M 69	0.3	1 "	Remained good	Decreased	Decreased	Decreased	" "	18 "	Severe leucopenia
11	F 39	0.26	17 days	Improved	"	—	—	—	14 "	"
12	M 55	0.35	8 "	"	"	Unchanged	Decreased	Fever and spinal pain decreased. Bone lesions unchanged	12 6	Leucopenia
13	F 64	0.3	1 day	"	Unchanged	—	—	Fever and abdominal mass decreased	Uncertain owing to subsequent x-ray therapy	"
14	M 41	0.2	1 "	Improved	"	—	Decreased	Spinal pain decreased	7	Interval of 7 weeks between doses
		0.2	1 "	Unchanged	"	—	"	" "	1	Severe leucopenia followed
15	M 21	0.18	10 days	Improved	"	—	—	Chest pain decreased	8	Leucopenia
		0.3	1 day	Unchanged	"	—	—	—	Nil	Leucopenia; died 1 month thereafter
16	M 36	0.06	4 days	Improved	Decreased	Unchanged	—	Chest effusion unchanged	6	Severe leucopenia; died 5 months thereafter
17	M 16	0.25 0.4 0.4	3 " 3 " 3 "	Remained good	Improved	Unchanged	Improved	Fever decreased	5	2 doses within 1 month
		0.4	3 "	Remained poor	—	—	—	Fever decreased	Nil	Severe leucopenia
18	M 55	0.3	1 day	Remained good	—	—	—	Spinal pain decreased	6 still well	
19	F 24	0.3	1 "	Improved	Unchanged	—	—	Chest effusion unchanged	8	Died 4 months thereafter
20	F 17	0.8	34 days	Unchanged	Decreased	Unchanged	Decreased	Pleural effusion and spinal pain decreased. Bone lesions and fever unchanged	Nil	Severe leucopenia
21	M 24	0.42	14 "	"	Unchanged	"	—	Fever decreased	"	Died 3 weeks thereafter
22	M 44	0.22	3 "	"	—	—	—	Jaundice and oedema unchanged	"	

TABLE IV.—*Chronic Lymphoid Leukaemia Treated with Oral T.E.M.*

Case No.	Sex and Age	Initial W.B.C.	Dose mg./kg. Initial Course	Lowest W.B.C.	Total Dose mg./kg.	Effect on Hb	Effect on Spleen Size	Effect on Node Size	Clinical Result
23	M 73	204,000	0.50	2,800	0.50	Rise	Decrease	Decrease	Satisfactory remission 8 months. Remains well. W.B.C. 28,000
24	F 55	223,000	0.18	21,400	0.48	"	Unchanged	Unchanged	Remission 2 months. Subsequent irradiation, with remission 4 months
25	M 75	23,500	0.10	3,300	0.10	"	Decrease	Increase	Satisfactory remission 5 months. Recent condition unknown
26	F 66	88,500	0.20	66,000	0.40	"	"	Decrease	Satisfactory remission 6 months. Remains well. W.B.C. 32,000
27	F 61	65,000	0.10	71,000	0.40	"	Unchanged	"	Satisfactory remission 4 months. Remains well. W.B.C. 10,000
28	F 80	18,000	0.10	6,700	0.10	"	"	—	Follow-up under 3 months
29	M 60	16,000	0.15	3,300	0.30	"	Decrease	Unchanged	Remission 4 months. Deteriorating. W.B.C. 10,000

TABLE V.—*Chronic Myeloid Leukaemia Treated with Oral T.E.M.*

Case No.	Sex and Age	Initial W.B.C.	Dose mg./kg. Initial Course	Lowest W.B.C. After Initial Course	Total Dose mg./kg.	Effect on Spleen Size	Clinical Result
30	F 54	189,000	0.40	8,900	0.80	Decrease	Remission 6 months. Remains well. W.B.C. 11,000
31	F 58	89,000	0.60	14,900	0.90	"	Remission 5 months. Remains well. W.B.C. 26,000
32	F 37	25,400	0.10	12,000	0.20	Increased	Died 4 months
33	F 44	54,000	0.15	7,000	0.55	"	" 3 "
34	F 58	47,000	0.40	36,000	0.40	Unchanged	" 1 month
35	F 64	249,000	0.55	2,900	1.35	"	" 7 months
36	F 64	198,000	0.45	26,500	0.95	—	" 7 "

cytopenia and petechial haemorrhages occurred, necessitating blood transfusions. The response to repeated transfusions of fresh whole blood has been good.

These six cases have been studied in the hope of illuminating the conditions under which severe leucopenia may occur. In one case no explanation could be advanced for the severe response. In another (Case 20) the occurrence was most likely due to the large dosage administered (0.8 mg./kg. in 34 days). Two patients had low polymorph counts before treatment; Case 3, for example, had a polymorph count of 2,500, although the total white count was 8,700. Case 16 also had an initial polymorph count of 2,100, with a shift to the left. Because his total white count was less than 4,000 the dose given was exceedingly small (0.06 mg./kg.); nevertheless, a severe leucopenia followed. Over a period of eight years this patient had had repeated x-ray treatments to enlarged lymph nodes and had been treated with nitrogen mustard one year before the treatment in question. His leucopenia was of long standing, but had never been severe with previous treatments.

In two cases the leucopenia might be ascribed to a cumulative effect. Case 14 was given two treatments with a seven-weeks interval. No leucopenia followed the first dose, the blood count being apparently satisfactory. The second dose of 0.2 mg./kg. produced the most serious leucopenia and thrombopenia we have encountered. This was shown in the bone marrow as a total reduction of cellularity. Case 17 developed leucopenia after the fourth dose within five months. Prior to this dose the polymorph count was high. The condition of the patient had, however, deteriorated. Further work is required to determine more accurately the factors responsible for these unexplained responses.

On the basis of these observations we now feel it is inadvisable to use T.E.M. in patients who have a low initial polymorph count.

From the point of view of avoiding severe leucopenia there has not seemed to be any real advantage in spreading the dose over several days, since the effects on the white-cell count do not become apparent until an interval has elapsed which has its median between the 14th and the 17th day after treatment. The cases which developed severe leucopenia did not show any shortening of this period, and the range of intervals was the same for those which had only a moderate effect on the white-cell count. This median interval of 14 to 17 days and the range found are strictly comparable to those following intravenous administration of the drug at appropriately lower doses.

In reviewing the cases it seems that a single dose of 0.3 mg./kg. should not be exceeded even if patients are under careful supervision. A slight reduction in the dose to 0.25 mg./kg. might be an advantage in allowing for the sensitive individual. At 0.3 mg./kg. more than half the patients will show leucopenia, in most cases slight. It is inadvisable to use the drug if the initial polymorph count is low.

For the management of our patients we have generally admitted them to hospital. The drug has also been given to out-patients; in these circumstances the patient has reported back at weekly intervals for a blood count and has been told that he should be prepared to come into hospital should the white-cell count be unsatisfactory.

Chronic Leukaemia

Seven patients with lymphoid leukaemia and seven patients with myeloid leukaemia have been treated by oral T.E.M. Summaries of the results in these cases are given in Tables IV and V. There seems to be a wide variation in the sensitivity of the leucopoietic system to T.E.M. in the chronic leukaemias, particularly in the lymphoid type.

In the first patients treated a daily dose of 1 mg. was given until a response in the blood picture was noted. This method was abandoned when it became apparent that a

severe drop in the white-cell count and platelet count might follow even when the administration of the drug was stopped as soon as the white-cell count began to fall. Latterly it has been our practice to administer a dose of 0.1 to 0.2 mg./kg. and to follow this by similar doses, given at intervals determined by the response. The interval between treatments should not be less than 14 days.

During the initial treatment with T.E.M. patients have remained under observation in hospital, but for subsequent maintenance treatment they have attended at monthly intervals. It has been thought unwise to let patients take supplies of this drug home, and each dose has been given in the light of the patient's clinical and haematological condition.

Chronic Lymphoid Leukaemia

There was a definite symptomatic improvement in five out of the seven patients with lymphoid leukaemia; in four the spleen was reduced in size and in three the nodes became smaller.

No attempt has been made to keep the total white-cell count within normal limits. The decision to give or withhold treatment has depended as much on the symptoms as on the leucocyte count. With this mode of treatment erythropoiesis does not seem to have been adversely affected and, as will be seen in Table IV, the haemoglobin levels have increased.

FIG. 1.—Case 23. Haemoglobin and white-cell counts.

Case 23 (Fig. 1).—A man aged 73 was first seen at this hospital with large nodes in all areas; these had been present for eight months. The spleen was enlarged to the umbilicus. Haemoglobin, 8.6 g./100 ml.; W.B.C., 350,000 per c.mm., mainly lymphocytes. He received single exposures of x rays to each side of the neck and each axilla, which resulted in a slight reduction in the size of the nodes in these areas. Four months later he developed signs of superior mediastinal obstruction. He was treated with an initial course of T.E.M. to a dose of 0.5 mg./kg., and this resulted in a fall in the W.B.C. from 204,000 to 2,800 per c.mm. in 58 days. During this period the largest neck node was reduced from 5 to 2 cm. in diameter, axillary nodes 5 and 6 cm. in diameter became impalpable, and the spleen was reduced in size. The dyspnoea and dizziness initially present disappeared and the mediastinal nodes were shown on radiological examination to have decreased in size. Eight months after treatment he was without symptoms but the nodes were again increasing in size. Haemoglobin, 13.6 g./100 ml.; W.B.C., 28,000 per c.mm.

It is probably fair to conclude that the result obtained with T.E.M. in this case was superior to that which would have been obtained by further radiotherapy, since the local response in the nodes to single exposures of 400 r and 800 r was disappointing.

T.E.M. is not, however, always superior to x-irradiation, as Case 24 illustrates. The dose of T.E.M. was probably low, but in our opinion this does not explain the longer remission obtained by splenic irradiation at a later stage of the disease.

Chronic Myeloid Leukaemia

Five out of the seven patients treated have died. They were all advanced cases that had already been treated with x rays or urethane, or both. At the best only transient remissions were obtained with T.E.M. In two patients who had not been previously treated, maintenance treatment has resulted in clinical and haematological improvement.

FIG. 2.—Case 30. Showing reduction of size of liver and spleen, and haemoglobin and white-cell counts.

Case 30 (Fig 2).—A woman aged 54 presented with lassitude, cramp in her legs, and a painful lump in her left loin. On examination the main findings were pallor, a palpable liver, and a spleen extending 7 cm. below the umbilicus. Haemoglobin, 10 g./100 ml.; W.B.C., 189,000 per c.mm.—polymorphs 127,500, lymphocytes 10,500, mononuclears 2,000, eosinophils 8,000, basophils 8,500, blasts 5,500, promyelocytes 13,000, myelocytes 9,500, metamyelocytes 4,500. The initial course of T.E.M. consisted of a dose of 0.4 mg./kg. given over 21 days. On discharge from hospital six weeks after admission the white-cell count was 8,900 per c.mm. and the haemoglobin 11.2 g./100 ml. The spleen extended only a centimetre below the umbilicus. She was free from pain. Maintenance treatment with T.E.M. has been given, and when last seen six months after the beginning of treatment the total white count was 11,100 per c.mm. and the haemoglobin 12.7 g./100 ml. The spleen had been reduced further in size, and was now confined to the left upper quadrant of the abdomen. The liver was not palpable.

Case 31.—A woman aged 58 was first seen at this hospital complaining of swelling of the abdomen for about a year and lassitude for three months. The spleen was extended below the umbilicus and the liver was palpable. Haemoglobin, 9.3 g./100 ml.; W.B.C., 89,000 per c.mm. The differential count and the sternal marrow confirmed the diagnosis of myeloid leukaemia. T.E.M. was given in repeated doses of 0.1 mg./kg. after an initial course of 0.6 mg./kg. given over 51 days. Since discharge from hospital maintenance therapy has been pursued. When last seen five months after beginning treatment she was symptomatically improved and the spleen was much reduced in size. Haemoglobin, 11.8 g./100 ml.; W.B.C., 26,000 per c.mm.

It is clear that the results obtainable in advanced cases of myeloid leukaemia are poor. The two satisfactory cases (Nos. 30 and 31) were previously untreated; it is just in such patients as these that splenic irradiation or urethane treatment leads to remissions of many months.

Miscellaneous Types of Malignant Disease

No beneficial effect was obtained from the use of oral T.E.M. in two cases with carcinoma of the breast, in both of which secondary deposits continued to grow after treatment. One of these cases was given a very high total dosage of 0.9 mg./kg. spread over 22 days. No significant leucopenia occurred; the haemoglobin was unchanged and the platelets remained abundant.

Two patients with proved radio-resistant tumours also failed to respond. One had widely disseminated malignant synovium; the other was a moribund patient with metastases from a malignant teratoma of the testis.

The only patient with polycythaemia vera was given a single dose, 0.25 mg./kg., and did not show any reduction in the red-cell count over the following six weeks. He was then given P³² and responded after two doses each of 5 mC, the reduction occurring eight weeks after the initial dose. Lack of response to T.E.M. in this case is contrary to the results obtained in other cases with intravenous use of the drug. It is possible that the dose was insufficient or that enough time was not allowed in which to observe the effects.

The only cases apart from Hodgkin's disease and chronic leukaemia in which we have observed some benefit were both reticulo-endothelial in type. One was a case of a typical lymphofollicular reticulosis in which a dosage of 0.25 mg./kg. given over three days produced a regression of lymph nodes in the mediastinum and elsewhere, and atelectasis of a lung lobe slowly cleared up. Another patient with a generalized reticulosis, which could not be classified, showed a partial response in the mediastinal nodes after a single dose of 0.3 mg./kg.

Summary and Conclusions

This contribution to the palliative treatment of chronic malignant disease is an extension of the investigation of triethylene melamine, which has been used both intravenously and orally with moderate success in certain diseases.

The clinical trial of a new substance presents difficulties. One is the very advanced stage of the disease in those patients selected for treatment. Another is the choice of dose level; this is not infrequently discovered in retrospect to have been inadequate or injudicious. Nevertheless the trial of enteric-coated tablets has revealed a reasonable consistency between dose and effect when dosage is given on a weight basis.

A beneficial effect has been obtained in Hodgkin's disease, in chronic leukaemia, and in two other cases of reticulo-endothelial disease; no good effect has been obtained in the tumours of epithelial or connective-tissue origin. This finding corroborates previous reports on the scope of the drug when it was administered intravenously at suitably lower dosage.

In Hodgkin's disease we have found that a dose between 0.2 and 0.3 mg./kg. given either undivided or spread over two or three days is suitable. Treatment should not be given in the face of a leucopenia induced by previous treatments by other agents. Repetition of the treatment is possible, provided that the polymorphonuclear leucocyte count is fully restored.

The possibility of latent damage to the haemopoietic system should be borne in mind; this was illustrated by the fate of one of the experimental dogs given a second treatment and by the serious leucopenia which occurred in one of our cases of Hodgkin's disease after a second small dose.

In chronic leukaemia the dosage has been administered at a lower level of 0.1–0.2 mg./kg. and has been repeated at intervals of several weeks for maintenance.

It has been notable that the response of cases of lymphoid leukaemia has been better than that of the myeloid cases. This is probably true even when allowances are made for the small numbers and the varied clinical condition of the patients. This finding has been encouraging, since with most other therapeutic agents the response of lymphoid leukaemia has been less favourable than that of myeloid leukaemia.

Tests of renal and hepatic function have not revealed changes after treatment, and post-mortem examinations, although often demonstrating long-standing damage or infiltration by disease, have not shown signs which could be definitely interpreted as due to toxic effects from treatment.

The haemopoietic system is highly sensitive to triethylene melamine, the effects being seen on the lymphocytes, granulocytes, and platelets of the peripheral blood.

The simplification of dosing by oral administration of enteric-coated tablets has seemed to be a worth-while advance; nevertheless by its very simplicity it carries a certain danger of being used without the essential haematological controls.

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TUBERCULOSIS CASE-FINDING BY THE TUBERCULIN-TESTING OF INFANT- SCHOOL CHILDREN

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"On numerous occasions, only the tuberculin reaction of a child or adult has revealed unsuspected infectious cases among his associates."—J. A. MYERS, Minnesota.

Several years ago one of us (Tattersall, 1946) expressed the opinion that tuberculin-testing of young children should be more extensively used for case-finding in this country. Several interesting cases of tuberculosis had been discovered in this way. For example, the mother of two tuberculin-positive children was able to give a thorough account of the social contact of her daughters aged 5 and 3, which suggested that the only association they had had with anyone liable to cough was their father, who for the past year had been in Hong Kong. A message was sent advising that he should have his chest x-rayed, and he was invalided home with consumption.

This experience, after various trials and errors, led to the more extensive tuberculin survey of all the infant-

school entrants in Bournemouth during the Michaelmas term of 1951, on which a preliminary report has been published (MacDougall, Mikhail, and Tattersall, 1951). Circumstances for this work had become propitious: the mortality rate from all forms of tuberculosis in Bournemouth during 1950 had fallen to 33 per 100,000 of population, the milk cleanliness in the town was known to have been good for a number of years, and the whole-hearted co-operation of all parties concerned could be anticipated. It was decided to test about 2,000 children over a period of about ten weeks which would cover almost all the children in the infant schools who had not yet reached their sixth birthday, including all the school entrants.

Since 1947 at least 97% of the milk sold in this county borough has been heat-treated, pasteurized, or from tuberculin-tested herds, and by the end of 1951 100% pasteurization had been attained. During the past five years all milk samples tested have complied with the current prescribed standards under the regulations of the Milk Special Designations Act, 1949; and under the Food and Drugs (Milk, Dairies, and Artificial Cream) Act, 1950, the town is shortly to become a "specified area" for the retail of "designated" milk. It therefore seemed reasonable to assume that a child beginning school and found to be tuberculin-positive would have been infected from a human source. The majority of such children would have led relatively sheltered lives, being too young to have had many casual stray and unknown contacts, so that any child thus infected would probably have incurred the infection within its own immediate family circle. The Michaelmas term survey was therefore designed to seek out and examine as exhaustively as possible all the relatives and friends (especially the adults) of tuberculin-positive school entrants.

A second survey during the Lent term was designed for comparison with the Michaelmas survey. A comparable number of infant-school children were tested, and their contacts examined, but by a slightly different procedure. This paper describes the methods and results of both surveys.

The Tuberculin Test

It was thought that the Mantoux test would require the positive written consent of a parent; so it was decided to proceed with the jelly test and advise parents that the test would be applied unless they objected. This was amply justified, since the success of the work depended on the co-operation of the family contacts of tuberculin-positive children. The technique used was that described by Dick (1950), and adopted for the Medical Research Council National Tuberculin Survey (1952), although later, suspecting the incidence of positive reactors might be unduly low, a slight modification recommended by Lendrum (personal communication) was adopted—namely, reading the results on the fourth day instead of the third day after application of the test. Flourpaper abrasion of the skin was not used on children under 6 years of age. In the Michaelmas survey whenever the result of the jelly test was doubtful a Mantoux test was performed, so that we always had a definite result; parental consent for this was obtained at the reading of the jelly test.

Organization of the Michaelmas Survey

1. The medical officer of health obtained the permission of the Education and the Health Committees for the investigation, and the scheme was explained to the head teachers of the schools involved.

2. The Public Health Department forwarded printed letters in stamped sealed envelopes to the school, from which