Section of Medicine

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DISCUSSION ON THE CHEMOTHERAPY OF THE RETICULOSES

Dr. John F. Wilkinson: I propose to consider the treatment of Hodgkin's disease, the leukæmias, and those other less frequently seen reticuloses, some of which are closely related to or may even be manifestations of certain acute leukæmias. It is most disturbing to note the increasing frequency of these conditions during the last twenty years or so.

Thus, from the Registrar-General's statistics the deaths from Hodgkin's disease have shown a slowly progressive increase in frequency, for example, from 566 (367 males and 199 females) in 1940 to 663 (414 males and 249 females) in 1950. There have been similar increases in the death-rates of other reticuloses, but the most disquieting of all has been the death-rate for the leukæmias which has increased from a total of 446 in 1921 to 1,832 in 1950. This is the common experience of all who see large numbers of these cases in their clinics, and it is certainly not due to more accurate diagnoses.

My chemotherapeutic investigations were carried out on 420 patients with acute or chronic leukæmias, Hodgkin's disease, or other forms of reticuloses.

Chemotherapeutic Agents

Apart from the earlier pre-war trials of arsenic, benzene, and similar substances, the present-day chemotherapeutic treatment of the reticuloses really has its origin in wartime research work which we commenced in Manchester in 1942. Originally at the request of Sir Edward Mellanby, then Secretary of the Medical Research Council, I had a small team working on and supervising the hæmatological changes occurring in workers engaged in the preparation and manufacture of chemical warfare agents of which the most interesting to us were the β-halogenated alkylamine type of vesicants popularly known as the nitrogen mustards. It was soon apparent to us that a profound depression of the leucocytes in blood and marrow was produced by exposure to these substances and led to my trying some of these β-chloro alkylamine series of agents intravenously on patients with initially high leucocyte counts (i.e. chronic leukæmias). This work was carried out at the Manchester Royal Infirmary. Chronic myeloid and lymphatic leukæmias, and later Hodgkin's disease, were found to be very sensitive to small doses of some of these agents (Wilkinson and Fletcher, 1947). Other research work has been continued actively since that time, but for reasons of security we were not able to publish the work until long after the end of the war. Many groups of workers have since confirmed my original observations.

Of all the substances tested at that time

tri-(2-chloroethyl)-amine hydrochloride $(Cl.CH_2.CH_2)_3$: N. HCl.,

and di-(2-chloroethyl)-methylamine hydrochloride $(Cl.Ch_2.CH_2)_2$: $N.(CH_3).HCl$., were found to be the most valuable for the treatment of chronic leukæmias and Hodgkin's disease, and to a lesser degree, polycythæmia and rarer forms of reticuloses.

These substances, often referred to as the nitrogen mustards, have profoundly depressant effects on the leucopoietic tissues much earlier than any effects they may have on the red cell series so that leukæmias are more easily and effectively treated than polycythæmia.

TRI-(2-CHLOROETHYL)-AMINE HYDROCHLORIDE

Dosage and Technique

These two di- and tri-(2 chloroethyl)-amines in the form of their hydrochlorides are very soluble in water, in which they rapidly undergo firstly a reversible chemical rearrangement with the formation of very reactive ethylene-imonium derivatives which produce powerful nucleotoxic and cytotoxic

effects on enzyme systems and mitosis in rapidly proliferating cells; these intermediate derivatives undergo hydrolysis in aqueous solution but especially in the presence of weak alkali, being converted to relatively inactive chlorhydrins and chlorine-free hydroxyamines having no leucotoxic activity.

For this reason, it is obvious that solutions of the nitrogen mustards must be made up freshly at the time of their administration, and not by the dispenser some hours or days before.

In spite of their vesicant properties these amines, as their hydrochlorides, can be given safely, and without fear, intravenously in diluted solution. From a very long and extensive experience of these substances I can confirm that the tri-(2-chloroethyl)-amine hydrochloride is the better and more convenient of the two amines, extremely rarely causing phlebosclerosis. The di-compound shows a greater tendency to cause local thromboses.

While the original dosage employed was 0·1–0·2 mg./kg. body weight, I have found that for an adult 6 mg. is a convenient standard single dose that can be weighed out and stored in sterile dry ampoules ready for solution in sterile water immediately before use. This dose of 6 mg. may be repeated if necessary in say two to three days or longer according to the level of the leucocyte count, which is done daily. Further doses are given when the leucocyte count ceases to fall further after the previous dose, until the required level is reached.

We find that the most convenient method of giving this treatment is to set up an intravenous saline drip with a No. 1 needle (or No. 2 in small veins), running the saline in as fast as the small needle will permit. *Then, and only then,* is the 6 mg. of tri-(2-chloroethyl)-amine hydrochloride dissolved in 5–10 ml. water and injected through the drip tube into the flowing saline, and thus run into the vein; after two to three minutes of saline flow the procedure is complete. It is also usual to give some patients 1 tablet of Phenergan or Avomine, repeating it four hours later to prevent or reduce any nausea. The majority of these treatments are given in my *out-patient* clinics.

Sensitivity to these nitrogen mustards varies quite considerably in different patients; thus a single injection of 6 mg. may be quite adequate to reduce a high leucocyte count to normal levels for many months (*see* Fig. 1 in Gardikas and Wilkinson, 1952); in another case several doses may be necessary (*see* Figs. I–IV in Wilkinson and Fletcher, 1947).

Effects of Nitrogen Mustard Therapy

The clinical effects of this treatment are local and general.

Local.—With the tri-compound no serious local effects occur but the di-compound tends occasionally to produce local tenderness and thrombosis of the veins at the site of the injection. Leakages into the tissues may cause local inflammation, pain and necrosis. These local effects are usually due to faulty techniques and should never occur if the dilute solution is given by the drip technique.

General effects may be mainly transient headaches, nausea, anorexia. Nausea and vomiting in varying degree may occur in about 20% and 12% respectively of patients coming on about two to five hours later and passing off in a few hours; only 0·1% showed a temporary and symptomless moderate neutropenia. These effects can be controlled or reduced in severity by the use of Avomine, Dramamine, or anti-histamine drugs given at the time of the injections and repeated about four hours later.

Changes produced in the blood and marrow.—The most marked changes are seen in the reduction of the leucocyte count, the most sensitive cells being the immature or rapidly growing cells in marrow and blood. Consequently the total leucocyte count begins to fall rapidly about the second to fifth day from the first injection, the maximal effect being seen about the seventh to fourteenth day, but this may be delayed or accelerated by varying the dose in patients with differing sensitivities. The immature cells may disappear completely from the blood by this time. The platelet count shows a corresponding but much less degree of reduction while the red cell count and hæmoglobin usually remain unchanged, but later rise spontaneously in the chronic leukæmias as the leucocyte count falls. Corresponding changes are noted in the bone-marrow where depression of the leucopoietic tissues is most striking and where they may return to a normal appearance. Overdoses with these nitrogen mustards will produce aplasia of marrow or agranulocytosis, but we have not seen it happen in our cases. Because of these depressant effects on the leucopoietic tissues of patients with chronic leukæmia it is important to control the treatment by regular leucocyte and platelet counts—daily in the first place until the desired count is reached, and then depending on the frequency of the treatments and clinical condition. I personally do not give any specific treatment for chronic leukæmia if the leucocyte count is less than 15,000–20,000. The leucocytes of the normal individual show a similar sensitivity to nitrogen mustards. On the other hand, in Hodgkin's disease, other reticuloses and polycythæmia vera, the leucocytes are apparently much less sensitive to these therapeutic doses of nitrogen mustard so that it is usually quite safe to give them treatment with a total leucocyte count of only 5,000 or so.

Glandular enlargement (Table I).—After nitrogen mustard therapy the splenomegaly of chronic leukæmia or Hodgkin's disease regresses rapidly while the enlarged lymph nodes of chronic lymphatic leukæmia and Hodgkin's disease may diminish extremely quickly, often in the course of seven to fourteen days, and can be kept down with appropriately spaced doses. Similarly, deposits in bones may respond almost equally quickly.

TABLE I.—RESPONSES FOLLOWING NITROGEN MUSTARD THERAPY IN 126 CASES OF CHRONIC LEUKÆMIA

Sign or symptom	No. of patients in whom symptom or sign was present before treatment: Myeloid	Lymphatic	After treatment: Relieved Completely	Partially	Unrelieved
Splenomegaly	70		32	34	4
		22	8	12	2
Lymphadenopathy		48	15	29	4
Fatigability	76		39	28	9
		48	18	21	9
Anorexia	60		30	24	6
		30	15	9	6
Fever	12		5	3	4
		6	3	3	—
Sweating	30		24	—	6
		32	29	—	3
			Gain	No change	Loss
Loss of weight	72		52	9	11
		45	30	9	6

The Results of Treatment with Intravenously Administered Tri-(2-chloroethyl)-amine Hydrochloride

Acute leukæmias.—No beneficial effects have been noted except in those few patients that presented first with raised leucocyte counts; in these cases a single dose of this therapeutic agent was often sufficient to lower the total leucocyte count, prior to specific treatment with aminopterin or cortisone (*see* Table I in Gardikas and Wilkinson, 1952).

Chronic leukæmias.—Some patients, especially elderly ones with only very slowly progressive or stationary chronic lymphatic leukæmias, may be so mild in symptoms and signs that no treatment is needed. These have been omitted from this list. In general I have considered as indications for treatment of chronic leukæmia a poor deteriorating condition, anæmia, rising leucocytosis, weakness, fatigue, loss of weight, sweating, marked splenomegaly and glandular enlargement.

The duration of remissions between courses has varied from less than a month to more than two years in some patients (Table II) while a very high proportion of the patients showed complete or considerable relief from the symptoms and signs of the condition (Table I). This has been particularly noticeable where there has been marked splenomegaly, hepatomegaly and glandular enlargement in any or many parts of the body, all glands being affected simultaneously by the injections of the tri-compound. The survival of these patients compares extremely well with the published results of corresponding groups treated by irradiation (Table III) in other centres.

TABLE II.—CHRONIC LEUKÆMIA: DURATION OF REMISSIONS BETWEEN COURSES OF NITROGEN MUSTARD

Months	No. of cases
> 24	2
13–24	11
7–12	14
4–6	31
1–3	59
< 1	9

TABLE III.—CHRONIC LEUKÆMIA: AVERAGE SURVIVAL SINCE START OF TREATMENT

Reference	No. of cases	Treatment	Average survival (months)
Myeloid leukæmia			
Hoffman and Craver (1931)	71	Irradiation	31
Vogt (1949)	86	Irradiation	19
Wintrobe and Hasenbush (1939)	23	Irradiation	20*
Wilkinson (1953) this series	69	Nitrogen mustard	29 (2–57)
Lymphatic leukæmia			
Vogt (1949)	65	Irradiation	19
Wilkinson (1953) this series	41	Nitrogen mustard	26 (1–34)

*Since diagnosis was established.

Hodgkin's disease (Table IV).—The dosage was controlled by the size of the glands, spleen or liver, and not by the relative insensitivity of the leucocytes to these therapeutic doses, in contradistinction to the hypersensitivity of the leucocytes in the chronic leukæmias. The effects of nitrogen mustard on Hodgkin's disease were most dramatic in most cases for the glands regressed rapidly so that in seven to fourteen days—sometimes less, according to dosage—in moderately severe cases they might be normal, or almost so. I have seen large masses of glands in neck, axilla, groin and mediastinum disappear in an incredibly short time without untoward incident, and I have also records of bone metastases clearing up with equal rapidity.

Recurrences frequently take place but again respond to further treatment. The only type that really fails is the young patient 15–30 years of age with a severe Pel-Ebstein syndrome, sweating profusely and continuously, but these patients do badly with any form of treatment.

7 patients with other reticuloses, 1 with lymphosarcoma, 6 with monocytic leukæmia showed only temporary partial remissions on adequate treatment (Table IV).

TABLE IV.—RETICULOSES

Tri-(2-chloroethyl)-amine hydrochloride

	No. of patients	Total dosage (mg.)	Regression of Splenomegaly	Enlarged lymph nodes	Survival (weeks)
Hodgkin's disease ..	54	6–174	Complete in	Complete in	
			1 week – 6	1 week – 6	
			2 „ –15	2 „ –15	16–404
			3 „ –17	3 „ –19	(5 2 years)
			4 „ – 3	4 „ – 5	(18 1 year)
			Partial – 9	Partial – 5	
			None – 4	None – 4	
Reticuloses (miscell.)..	7	12–30	Temp. partial.	Temp. partial	2–17
Lymphosarcoma ..	1	108	Temp. partial	Temp. partial	56
Monocytic leukæmia..	6	12–30	None – 5	None – 5	1–12
			Partial – 1	Partial – 1	Alive (52 weeks)
Myelomatosis.. ..	2	12–30	—	—	Treatment changed

β-NAPHTHYL-DI-(2-CHLOROETHYL)-AMINE (R.48)

The search for a satisfactory preparation that can be given orally led Professor Haddow and colleagues (1948) to produce a series of substances of which one,

β-naphthyl-di-(2-chloroethyl)-amine, (Code No. R.48)  $-N:(CH_2.CH_2.Cl)_2$

seemed worthy of trial, and he kindly made it available to us and others through the Medical Research Council (Gardikas and Wilkinson, 1951). It proved on the whole disappointing and distinctly inferior to the tri- and di- (2-chloroethyl)-amines given intravenously; it was found, however, to have some value in certain cases, especially of Hodgkin's disease, over long periods and for patients with poor veins. It is a milder, and less toxic substance.

The dosage employed was 50–800 mg. in divided doses daily orally, the more usual quantity being 100–300 mg. daily. Occasional toxic effects were noted such as hæmaturia, dysuria, purpura, and occasional nausea or diarrhœa, but these had no relationship to the amount or frequency of treatment.

The results of treatment were variable as will be seen from Table V but, in general, R.48 was of no value in any of the acute leukæmias, or lymphosarcoma. In chronic leukæmia (10 myeloid; 12 lymphatic) 3 of the 10 myeloid leukæmias showed good responses, living one and a half, two and three

TABLE V.—TREATMENT WITH β-NAPHTHYL-DI-(2-CHLOROETHYL)-AMINE (R.48)

	No. of cases	Daily dose (mg.)	Total amount given (grammes)	Regression of glands and spleen (days)	Response to treatment: Good	Fair	None	Toxic effects
Hodgkin's disease	19	50–300	2–45	50–150	5	8	6	Transient maculo-papular rash (2)
Chronic myeloid leukæmia ..	10	50–400	5–300	50–100	3	3	4	
Chronic lymphatic leukæmia	12	50–400	3·6–28	20–60	3	4	5	Hæmaturia (1); Dysuria (1); Purpura (1)
Acute myeloblastic leukæmia	2	400–800	6·8; 21·6	—	—	—	2	—
Acute lymphatic leukæmia ..	1	50	2·0	—	—	—	1	—
Mycosis fungoides	2	100–400	5–10	—	1	1	—	—
Lymphosarcoma	2	200–400	8–12	—	—	1	1	—

years respectively, and 3 fair responses to treatment, while 4 failed to benefit at all. Of the 12 lymphatic leukæmias, 3 gave good clinical responses, 2 being still alive after fifty-five and eight months respectively, while 4 showed fair improvement but 5 did not improve on R.48. 19 patients with Hodgkin's disease were treated; 5 showed good responses, and 8 fair improvement for a time on doses of 50–300 mg. daily, the spleen and glands showing marked or complete regression in size in fifty to one hundred and fifty days.

Urethane

Urethane (ethyl carbamate, $NH_2.CO.OC_2H_5$) has been found to have marked depressant effects on the bone-marrow and especially on the leucopoietic elements in chronic leukæmias. It is given in doses of 1–3 grammes daily, the dose being reduced as soon as possible to the minimum as the leucocyte count falls; the spleen and lymph nodes may be reduced, but urethane has a very disconcerting way of suddenly producing aplastic anæmia, agranulocytosis or severe thrombocytopenic purpura after a variable interval of some weeks or months of apparently good control of the leukæmic process; proper control must be maintained by weekly determinations of the full blood count and platelets—leucopenia or thrombocytopenia may be the first sign of complete, irreversible marrow failure. Urethane has little value in the treatment of Hodgkin's disease, acute leukæmias, or other reticuloses, but I have produced relief of pain, temporary healing and regression of the bone changes and slowing of the disease process in 3 patients with multiple myelomatosis—1 is still alive after eighteen months of treatment having taken 697 grammes of urethane in that period (Table VI).

Table VI.—Urethane

Disease	No. of cases	Total dosage (grammes)	Survival (months)	Therapeutic effects
Hodgkin's disease	3	30–50	1–2	None
Chronic myeloid leukæmia ..	14	4–876	1–31	Temp. incomplete Aplastic anæmia
Chronic lymphatic leukæmia ..	5	2–430	1–14	Agranulocytosis Thrombocytopenia
Monocytic leukæmia	4	36–214	1–6	None
Acute myeloid leukæmia ..	6	1–126	3(days)–8	None
Acute lymphatic leukæmia ..	3	3–48	1(day)–3	None
Myelomatosis	4	4–[697]	2(days)–[18]	Relief pain. Temp. healing. Slowing of disease (3)
Other reticuloses	5	30–100	1–2	None

Aminopterin

I have dealt very fully with the folic acid antagonists, in particular aminopterin, in a lecture in 1947 to the Section of Experimental Medicine (Wilkinson, 1948; Wilkinson and Gardikas, 1951) and need only refer to the report on the beneficial effects of the folic acid antagonists in children with acute leukæmia (Farber, 1949; Farber *et al.*, 1948). Since then varying experiences have been described by other workers with generally disappointing results. In our hands aminopterin did not prove to be of any value in the treatment of the chronic leukæmias, Hodgkin's disease and other reticuloses. Of patients with acute leukæmia, 28 acute myeloblastic, lymphatic and monocytic leukæmias failed to respond to its influence, but 8 showed partial remissions (twenty to sixty days), and 2 complete remissions for up to sixty-two days (Table VII). The dosage employed was 1 mg. orally or subcutaneously daily or on alternate days until toxic manifestations or severe leucopenia developed. The chief toxic features were stomatitis, diarrhœa, hæmorrhagic rashes, epistaxes, alopecia, and leucopenia with thrombocytopenia, but it is difficult to be certain whether some of these were not part of the acute leukæmia itself (Wilkinson and Gardikas, 1951). While disappointing in their ultimate effects, nevertheless in co-operation with other agents (e.g. ACTH, and cortisone) better results have been obtained.

Cortisone and ACTH

Many varied opinions have been expressed as to the value of these hormones in the treatment of leukæmias, reticuloses, and allied conditions. In general our experience has been disappointing in view of the perhaps extravagant claims that have been made by others. The experience of the Hæmatology Panel of the Medical Research Council (1952) did not lead to the feeling that these hormones were of much value in the treatment of disorders of the blood, and of the reticuloses; only some of the acute leukæmias in children seemed to show temporary partial remission.

In my group of patients we found that there were no beneficial effects following the administration of these hormones in chronic leukæmias, Hodgkin's disease, myelomatosis, and other reticuloses (Table VIII). Of the acute leukæmias, 28 patients failed to show any improvement (Table IX). On

TABLE VII.—ACUTE LEUKÆMIA: PARTIAL OR COMPLETE REMISSION FOLLOWING AMINOPTERIN

Case No.	Sex	Age	Type of leukæmia	Total dose (mg.)	Length of remission (days)	Duration of leukæmia since treatment began (days)
				Partial Remission		
1	M	6	Myeloblastic	17	20	75
2	M	13¾	„	Met-Fol.B 100 + aminopterin 6	60	120
3	M	4	„	3	20	60
4	F	5	„	(*a*) 5 (*b*) 10	(*a*) 42 (*b*) —	113
5	F	4¼	Lymphatic	3	30	77
6	F	2¾	„	(*a*) 5 (*b*) 3	(*a*) 60 (*b*) —	172
7	M	5½	Monocytic	14	60	264
8	F	7	„	5	34	72
				Complete Remission		
9	M	15	Myeloblastic	15	30	63
10	F	2¼	Lymphatic	(*a*) 9 (*b*) 5	(*a*) 62 (*b*) 60	187

TABLE VIII.—RETICULOSES: ACTH OR CORTISONE

Case	No.	Total dosage	Therapeutic effects	Duration of life (weeks)
Hodgkin's disease	6	ACTH 500–2,000 Cortisone 700–2,000	None	—
Follicular lymphoblastoma ..	2	ACTH 1,400–2,805 Cortisone 1,000–1,600	Poor or none	1–32
Myeloid reticulosis	4			
Acute reticulosis	3			
Reticulum cell reticuloses ..	1		Slight temp. improvement	14
Chronic leukæmia	5	Cortisone 750–2,000	None	—
Acute leukæmias (rare types)	6	ACTH 500–1,500 i.m. ACTH 100 i.v. Cortisone 1,000	None	1½–10
Mycosis fungoides	3	Cortisone 1,000–2,000	Partial	—
Myelomatosis	3	ACTH 1,400–2,000	None	3–4

TABLE IX.—ACUTE LEUKÆMIA: NO RESPONSE TO CORTISONE OR ACTH

	Cases			Age		Total dosage (mg.)	Start of treatment to death (days)
	Male	Female	Total	Male	Female		
Acute myeloblastic leukæmia ..	8	5	13	4–40	5–47	A/120–2,400 C/250–1,300	5–150
Acute lymphatic leukæmia ..	8	2	10	3–62	8–61	A/200–2,500 C/100–1,600	6–21
Acute monocytic leukæmia ..	4	1	5	10–64	65	A/300–850 C/720–2,000	5–40

A=ACTH
C=Cortisone

the other hand, 16 patients have shown partial or complete remissions temporarily, but relapsed later (Table X); in general, the child with acute lymphatic leukæmia and no gross splenomegaly does the best. 3 of these patients showed full and complete remissions and are alive and well at the present time of writing—1 being completely normal clinically and hæmatologically in every way, and has been without any treatment for over twelve months.

TABLE X.—ACUTE LEUKÆMIAS RESPONDING TO CORTISONE OR ACTH

Case	Total dosage mg.	Response to treatment	Splenomegaly lymph nodes	Duration of life from treatment to death (weeks)
	Acute Myeloblastic Leukæmia			
M 7	C. 1,000	Partial		10
M 5	(1) A. 900 (2) C. 1,100	P nil	Regressed completely	15
F 56	C. 5,000	P	or considerably until	14
F 6	C. 1,000	P	relapse	17
M 3	(1) A. 480 (2) C. 900	P nil		31
M 16	(1) C. 3,000 (2) C. 3,200	Full	Complete regression with normal blood and marrow	Alive and normal (10 weeks) no treatment
	Acute Lymphatic Leukæmia			
M 6	A. 800	Partial		8
F 5	(1) A. 650 (2) A. 200 (3) C. 900	P		18
F 4	(1) A. 480 (2) C. 275	P	Regressed completely or considerably until	9
F 2½	C. 2,775	P	relapse	16
F 2¾	C. 1,200	P		14
M 5	C. 750	P		14
M 5	C. 2,700	P		Alive (13 weeks)
F 2½	C. 2,000	P		Alive (8 weeks)
F 5	C. 9,500	Full	Complete regression with normal blood and marrow	Alive and normal (76 weeks) no treatment
M 19	(1) A. 1,850 (2) C. 350	Full		33

1:4—DIMETHANESULPHONYLOXYBUTANE (G.T.41; C.B.2041; MYLERAN)

Myleran ($CH_3.SO_2.O.CH_2.CH_2.CH_2.CH_2.O.SO_2.CH_3$) is a substance that was kindly supplied to me for trial by Professor Haddow and his colleagues (Haddow and Timmis, 1953; Galton, 1953). As they had found, so we confirmed that it was only of value in the treatment of chronic myeloid leukæmia which can be fairly well controlled so far as our present knowledge goes. The dosage requires great care in adjustment—depending on the degree of leucocytosis; as originally suggested we gave an initial dose of 25 mg. orally for three to five days, and after the full effects had been developed in the course of two to three weeks a maintenance dosage of 2–4 mg. daily or on alternate days was given according to the then leucocyte count. Great care is needed in increasing or continuing the doses owing to the profound effects of this substance on all the elements of the marrow, producing in excess dosage aplastic anæmia, thrombocytopenic purpura and agranulocytosis. This is particularly liable to occur in chronic lymphatic leukæmia and other reticuloses for which it is of no value.

Most chronic myeloid leukæmias showed response to this treatment in the beginning, the spleen diminishing in size as the leucocyte count fell, but some patients failed to maintain improvement, developing anæmia or marrow aplasia, or just failing to keep the leukæmic process under control.

In our series 18 patients (6 males, 12 females) responded well in the beginning, and after intervals of five to fifteen months there had been good clinical responses in 15; 6 patients had leucocyte counts less than 10,000, and 13 had less than 30,000 leucocytes. Of these, 5 failed to maintain the improvement and relapsed with anæmia (after five and six months respectively), aplastic anæmia (eight months), hypoplastic anæmia (eight and a half months) or increased leucocytosis often with further enlargement of the spleen once again: 1 patient developed thrombocytopenia (ten months) but after discontinuance of treatment and several blood transfusions recovered, and is now well after fifteen months. 13 patients are still well and under control on doses of 2–4 mg. daily or alternate days. Splenomegaly diminished considerably in 12, slightly in 4, and not at all in 2.

TRIETHYLENE MELAMINE (T.E.M.)

This substance, which Dr. Nabarro is to discuss, is in our experience the most toxic of all the chemotherapeutic agents as yet tried—producing thrombocytopenia, aplastic anæmia, neutropenia or agranulocytosis in a large proportion of the cases receiving it in even quite small doses of 1–10 mg. orally or intravenously. Under no circumstances should it be made available for general use or ever employed without the most strict hæmatological control. In our experience its effects were variable in chronic leukæmias and Hodgkin's disease, but at least 50% of patients will show neutropenia, agranulocytosis or aplastic anæmia.

SUMMARY

The main features and effects of these chemotherapeutic agents are summarized in Table XI from which it will be seen that intravenous tri-(2-chloroethyl)-amine hydrochloride is very effective and can be easily controlled in the treatment of chronic leukæmias and most reticuloses; Myleran is of great value for chronic myeloid leukæmia, while urethane is also effective in some chronic leukæmias at least for a time. Aminopterin, ACTH and cortisone have been of value in some acute leukæmias, but of no value in other reticuloses and chronic leukæmias; triethylene melamine is too dangerous and toxic for safe use in these conditions.

TABLE XI.—CHEMOTHERAPEUTIC AGENTS

Agent	Effective dose	Toxicity	Therapeutic value	Toxic effects
Tri-(2-chloroethyl)-amine (Lekamin) Di-(2-chloroethyl)-methyl-amine	4–6 mg. i.v. as required	Slight in therapeutic doses	Chronic myeloid, and lymphatic leukæmia, Hodgkin's disease, some reticuloses	Some nausea, vomiting
β-Naphthyl-di-(2-chloroethyl)-amine (R.48)	100–800 mg. orally daily	Slight	Hodgkin's disease chronic leukæmia	Nausea, purpura, hæmatemesis, dysuria, diarrhœa
Urethane	0·5–3 grammes orally daily	Moderate variable	Chronic leukæmia	Aplastic anæmia, thrombocytopenic purpura, agranulocytosis
1:4-dimethanesulphonyloxy-butane (G.T.41; Myleran)	100–125 mg. orally	Marked	Chronic myeloid leukæmia	Aplastic anæmia, thrombocytopenic purpura, agranulocytosis
Triethylene melamine (T.E.M.)	1–10 mg. orally daily	Very marked	Variable—chronic leukæmia	Nausea, vomiting, diarrhœa, aplastic anæmia, agranulocytosis, thrombocytopenic purpura
Aminopterin	Up to 1·0 mg. orally or i.m. daily	Marked	Fair; variable in acute leukæmia	Thrombocytopenia, loss of hair, ulceration of mouth
Cortisone, ACTH	Up to 300 mg. daily	Slight	Fair; variable in acute leukæmia	Various

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Professor A. Haddow: The various chemical agents used in the treatment of the reticuloses induce their effects by very different means, (1) whether endocrine, as in the action of cortisone and ACTH in acute leukæmia, (2) through antagonism of a specific nutrilite, as in the case of the so-called folic acid antagonists also in acute leukæmia, (3) through an effect upon maturation, or differentiation, as for urethane in chronic myelogenous leukæmia and myelomatosis, and (4) by a more direct cytotoxic or cytostatic mechanism exemplified by the nitrogen mustards, both aliphatic and aromatic, and by other chemical types, more recently discovered and acting by the same or a similar direct mechanism, such as the polyethyleneimines and a new series devised by G. M. Timmis of which Myleran is a member, active in chronic myelogenous leukæmia. Members of the last type are believed to produce their effects through chemical alkylation of protein or nucleoprotein in the cell, and hence have come

to be known as "biological alkylating agents". This property is preponderantly directed against cells in an active state of division, whether malignant or not. Hence, in applying such agents we interfere not only with the division of the tumour cell but with that of many normal cells as well, especially in the bone-marrow and the reproductive organs. This recalls the opinion of J. A. Murray, the distinguished Director of the Imperial Cancer Research Fund, twenty years ago, when he doubted the possibility of our ever being able to suppress the growth of the cancer cell, without producing equivalent damage to normal cells at the same time. This lack of specificity still remains the most powerful limiting factor. The second lies in the fact that the tumour cells themselves, in all too many cases, soon become refractory to the inhibitory effect of the chemical agent, presumably through the selection of resistant forms, by the induction of drug-resistance, or by a combination of both. What I have to say will illustrate both these difficulties only too clearly. At the same time it should be realized that the chemotherapy of the reticuloses, as of cancer generally, is still in its veriest infancy.

Anything I have to say of clinical observations made at the Royal Cancer Hospital is entirely due to the work of my clinical colleagues there, and especially that of D. A. G. Galton.

Cortisone and ACTH in Leukæmia and Allied Diseases

Many workers, including Pearson, Farber, and Wintrobe, have reported on the use of ACTH and cortisone in acute leukæmia in both adults and children. On a dose of 25 mg. six-hourly in adults, and about half this dose in children, approximately 50% of cases may enter complete clinical and hæmatological remission. In these, chemical studies often indicate a mass destruction of leukæmic tissue. Great variation is observed from patient to patient in regard to the cytological, physiological and biochemical effects of the hormones. The remaining cases do not respond, even to much increased dosage, and those undergoing remission inevitably relapse either during treatment or after it, the great majority proving unresponsive to subsequent therapy. Pearson and his colleagues have also studied the effect of ACTH on the chronic lymphomas, including chronic lymphatic leukæmia, lymphosarcoma, Hodgkin's disease, and related conditions. During the period of investigation there was rapid regression of the lesions, but the underlying pathological conditions were not significantly changed, and the lesions rapidly returned when administration of ACTH was discontinued. In the opinion of Mickle, ACTH and cortisone are of less value than aminopterin in the treatment of acute leukæmia in children. Dameshek commenting on the recent report by the Hæmatology Panel of the Medical Research Council, says that in the acute and subacute leukæmias of infancy and childhood, the steroid hormones induce a well-defined and even a complete remission in about 50–60% of the cases. If ACTH or cortisone is given simultaneously with aminopterin a remission may be induced in almost every case. Although in most cases the remissions are not sustained for more than two to four months, in some cases excellent and even complete clinical and hæmatological remissions continue for a year or longer. ACTH and cortisone may also, not infrequently, be useful in chronic lymphocytic leukæmia. The difference of opinion is attributed largely to the dosage used: the cases referred to in the Medical Research Council report received 1 gramme ACTH and 1·5 gramme cortisone over ten days, whereas in Dameshek's opinion ACTH must be given in amounts of from 150–300 mg. daily, and even this is sometimes ineffective.

Antagonists of Folic Acid and of the "Citrovorum" Factor, in the Treatment of Acute Leukæmia

As for many other agents in cancer chemotherapy, interest in the so-called folic acid antagonists is divided between the fundamental problem of their mode of action and of their practical application. On the fundamental side Sauberlich in 1949 discovered that the *Leuconostoc citrovorum* factor is capable of reversing the effects of aminopterin, and the factor was identified and synthesized by Brockman and others in the following year. The reversal of aminopterin toxicity by the citrovorum factor has also been studied by Schoenbach, Cravens and Snell, Greenspan, Earle, and others, with support to the hypothesis that aminopterin interferes with the enzymatic conversion of folic acid to the citrovorum factor, as well as with the enzymes involved in the further metabolism of the citrovorum factor itself. Both folic acid and the citrovorum factor have close interrelations with the metabolism of purines, pyrimidines, nucleosides, nucleotides and nucleic acids; and from the work of Skipper and others it appears that the folic acid antagonists may conceivably operate through an inhibition of nucleotide synthesis.

From a great number of papers on the practical application of these agents, the results of therapy with aminopterin and its analogues such as amethopterin and aminoanfol appear to fall into three classes, namely, no response, temporary clinical improvement, and, in the smallest number, remarkable and complete remissions which usually last for a short period only, but which may on occasion be prolonged. Thus the most favourable results so far achieved in the treatment of acute lymphatic leukæmia in childhood have been obtained with aminopterin and related compounds, in the shape of remissions lasting over a year. Even though administration of these drugs is as a rule limited by the early development of toxic effects, it is remarkable that remission can be induced at all in such conditions, hence the fundamental importance of the observations themselves.

Urethane in Multiple Myeloma

Although urethane is capable of producing useful responses in chronic myeloid leukæmia, in which according to Whitby it may be as effective as, and less misery-making than, X-rays, it has almost certainly been superseded by Myleran. Longer remissions may be achieved by Myleran and these are not infrequently maintained for considerable periods even when the drug is withdrawn. The employment of urethane in multiple myeloma has been studied by Rundles, who describes how, as plasma-cell growth is inhibited by urethane, abnormal serum components are reduced or may virtually disappear. Rundles and his co-workers also mention an observation made in a case in which benefit from ten months' continuous urethane therapy was followed by relapse. When urethane was discontinued, the plasma cells in the marrow again decreased and proteinuria diminished, a phenomenon which these authors interpret as indicating that the prolonged exposure to urethane had rendered the plasma cells nutritionally dependent, so that their growth was once again inhibited by the drug's withdrawal.

Harrington and Moloney also report a number of cases of multiple myeloma treated with urethane, of which a proportion showed relief of pain, gain in weight, improvement in anæmia, reduction in abnormal serum proteins, suppression of plasma-cell proliferation and probable prolongation of life. A further series of 66 proved cases treated with urethane over a two-and-a-half-year period is provided by Luttgens and Bayrd. Again there is some over-all suggestion of prolongation of life. However, only 50% showed subjective improvement, and 20% objective improvement. While their results appear not as favourable as in other series, these authors believe the administration of urethane to be probably as good treatment as is available for multiple myeloma at the present time.

While urethane has doubtless been useful in a limited sense, again its main interest probably lies in its mechanism of action: this is still obscure, although much has been contributed by Skipper and his school employing labelled compounds—especially the suggestion that urethane may inhibit the incorporation of formate in nucleic acid synthesis.

The Nitrogen Mustards in the Therapy of Hodgkin's Disease, the Leukæmias and Reticuloses

Recognition that the nitrogen analogues of mustard gas, or the so-called nitrogen mustards, can induce cytotoxic effects in a wide variety of tissues, and especially those in a state of active proliferation, originated from the study of these substances as potential agents of chemical warfare. A remarkable feature of the mustards is the way in which they reproduce many of the biological effects of high energy radiations. Useful clinical responses are very largely confined to the spectrum of neoplastic disease involving the reticulo-endothelial system—the leukæmias, multiple myeloma, lymphosarcoma and reticulum-cell sarcoma, Hodgkin's disease, giant follicular lymphoblastoma, polycythæmia vera, mycosis fungoides, Boeck's sarcoid, and other but rarer allied conditions. The nature and extent of the response is preponderantly determined by the histogenesis of the tumour and by the inherent activity of the given compound, and cannot appreciably be improved by mere modification in technique of administration.

In the treatment of Hodgkin's disease, most workers express the opinion that nitrogen mustard therapy should not be regarded as an adequate substitute for irradiation, but should be reserved for cases with marked constitutional symptoms and visceral involvement. In these, a period of marked rehabilitation may follow the use of one or several courses, although opinion is doubtful whether, in fact, the advent of the nitrogen mustards has seriously, if at all, modified the basic prognosis. They may, however, be used with profit in cases for which radiotherapy is no longer suitable, and, in a proportion of those, surprisingly good responses may be obtained. They may also prove a valuable substitute for X-ray therapy in mycosis fungoides, and encouraging results, with prompt hæmatological and clinical responses, are frequently although not invariably observed in polycythæmia vera.

The nitrogen mustard most commonly employed is methyl-bis(β-chloroethyl)-amine or HN_2: the corresponding tri- compound HN_3 is more toxic but has been successfully used by Dr. Wilkinson in the treatment of the chronic leukæmias. Much labour and ingenuity have been spent in an endeavour to produce variants of enhanced therapeutic efficiency—at the Royal Cancer Hospital especially by the late Professor Kon, W. C. J. Ross, and others—and several aromatic derivatives are now available which have one advantage in that they can be administered for long periods orally, and produce no acute side effects. One of these, β-naphthyl-di(2-chloroethyl)-amine, has been extensively studied in clinical trial at the Royal Cancer Hospital and elsewhere, but with relatively disappointing results which indicate that it is less active than HN_2, slower in action, and produces remissions which are less in frequency and extent, and are of shorter duration, than those produced by the aliphatic nitrogen mustards. It may, however, be helpful in the treatment of polycythæmia vera.

Triethylene Melamine

Apart from their clinical application, much attention has been paid in the past few years to the more fundamental aspects of the action of the nitrogen mustards. On the basis of a correlation between biological activity and the presence in the molecule of a minimum of two reactive side-chains, Goldacre,

Loveless and Ross suggested that the biological effects of these substances might primarily be due to a process of chemical cross-linkage between the constituent molecular chains of the chromosome fibre. While this view is now known to be unduly simple, and other possibilities are equally likely, it has led to the general conception of the action of these and similar agents by virtue of the alkylation of genetic protein. In this way the hypothesis has provided a remarkable stimulus to the development of the subject and to the search for alkylating agents of increased therapeutic efficiency—for example, among various substances already utilized as cross-linking agents in the textile industry, among which many di-epoxides and polyethyleneimines have now been shown to possess cytotoxic activity of the same general type as that already known in the case of the mustards.

The triethylene melamine known as T.E.M. (2:4:6-triethyleneimino-*s*-triazine), is of special interest since it was originally devised by the Hoechst Farbwerke as a cross-linking agent of high efficiency, and was later described by Lewis and Crossley, and by Burchenal and others, as capable of retarding the growth of various mouse leukæmias and other tumours. The toxicity of this substance is about twice that of HN_2, and therapeutic responses are obtained in the range of from 8 to 12 mg. total dosage in the adult. Since it can be given intravenously without venous thrombosis or severe nausea or vomiting, and is therapeutically as active as HN_2, it has tended of late to supplant the latter in clinical practice. Rhoads and his colleagues have described how oral administration will induce temporary objective and subjective improvement in Hodgkin's disease and in chronic myelogenous and lymphatic leukæmia. Indications are similar to those for HN_2, and the slower and more prolonged action by oral administration may make it more useful. In 43 cases, Bayrd found results to be most favourable in chronic myelogenous leukæmia, less so in chronic lymphatic leukæmia, Hodgkin's disease and lymphosarcoma. Meyer studied 17 cases of chronic leukæmia treated in total doses of 10–125 mg. over periods of 10–200 days, in courses ranging from 10–20 mg. Complete hæmatological remissions occurred in 2 cases of chronic lymphatic leukæmia, but otherwise results were distinctly variable. Although in the hands of Paterson and Boland T.E.M. appeared equal to established methods of treatment in cases of leukæmia, polycythæmia, Hodgkin's disease, and myelomatosis, these authors did not regard it as in any way superior. Treatment must be extremely closely controlled to avoid serious depression of the marrow. Thus Shimkin points out the disadvantage of T.E.M.'s narrower chemotherapeutic range of dose, as compared with HN_2, and mentions that the oral dose in lymphatic leukæmia, which may be extremely sensitive, should not exceed 0·1 mg./kg. body weight. According to Hansen and Bichel, depression of the bone-marrow occurs later than with nitrogen mustard, lasts longer, and may sometimes be irreversible.

Our own experience over the past two and a half years has been limited to 20 cases of Hodgkin's disease and 14 of lymphosarcoma. Of the 20 cases of Hodgkin's disease, the majority were young adults, most had received X-radiation earlier, and all were in an advanced or generalized state of the disease, with toxic symptoms prominent. 8 were treated by the intravenous route and 12 by the oral. The maximum intravenous dose at one injection was 2 mg., and the maximum total i.v. dose 12 mg. The maximum single dose orally was 10 mg. and the average 5 mg., while the maximum total oral dose, and the maximum tolerated, was 50 mg. This is now known to be excessively high, since in one case agranulocytosis followed a total of 35 mg. in 5 mg. doses. Of the 20 cases, 12 obtained remissions lasting two to six months, of real value in most. Of these, 4 received 1 or more subsequent courses which were never as effective as the first. In 2, both of whom had also received further X-ray treatment, fatal aplasia of the marrow supervened. In general, the more satisfactory remissions appeared as good as those from HN_2, but subsequent courses appeared not only less effective but dangerous, seeming to render the patient liable to much greater marrow damage from subsequent X-rays.

Of the 14 cases of lymphosarcoma, 11 were treated by the oral route and 3 intravenously. The maximum intravenous dose at one injection was 2 mg., the maximum single oral dose 15 mg., and the maximum total oral dose 75 mg. Again this is much too high, since agranulocytosis followed administration of 20 mg. in four days in one case, and of 25 mg. in five days in another. Of the 14 cases only 2 showed useful regressions, the drug either producing no effect in the remainder, or regression accompanied by severe depression of the marrow.

In sum, and even allowing the advanced stage of the disease in most of these cases when treatment was started, our experience with T.E.M. has, in general, been depressing.

Myleran in the Treatment of Chronic Myelogenous Leukæmia

Following the detection of high tumour-inhibitory activity in various sulphonic acid esters synthesized by Timmis, it was decided that the correlation between chemical constitution and activity could best be studied by utilizing a simple structure to carry the functional groups, and one which would be easily capable of modification in regular gradations.

A series of dimethanesulphonyloxyalkanes was therefore synthesized, in which the number of carbon atoms in the central chain varied from 2 to 10. Biological activity is at a peak where $n = 4$ or 5. In the former case (1:4-dimethanesulphonyloxybutane), the compound has a specially

pronounced action on the granulocytes, which observation has led to its clinical trial by Galton in cases of chronic myelogenous leukæmia, to which its use would so far appear to be confined.

In a series of 19 patients to whom the substance was given orally, relief of symptoms, general improvement, regression of enlarged spleen, rise in hæmoglobin level, and fall in the leucocyte count with improvement in the differential count, have all been observed. While all cases responded initially, 9 relapsed within six months. However, 8 patients obtained remissions of 23 months, 18, 18, 15, 14, 13, 10 and 6 months respectively. The response in 3 patients who had received no previous treatment was comparable with the best results of radiotherapy. 5 of 9 patients for whom radiotherapy was not advised obtained useful remissions, and the remaining 4 outstandingly successful remissions. In 3 cases the response to Myleran compared unfavourably with what might have been expected of radiotherapy, but excessive dosage may have been responsible by causing irreversible damage to the marrow in 1 case and by leading to drug resistance in the other 2. Thrombocytopenia is the only important side effect, but is unlikely to be serious if large doses are avoided and if treatment is withheld when the platelet count is below 100,000.

The drug is more selective than the nitrogen mustards or the folic acid antagonists in its effect on myeloid cells, and may be somewhat safer in use: many cases have received daily doses by mouth of 4 mg. for several months. In such doses, although it depresses myelopoiesis, it has little effect upon the lymphocytes and platelets, and side effects are absent. Larger doses, however, depress the platelet count and cause hæmorrhagic symptoms, and there is a danger of causing an irreversible depression of the marrow which may not become obvious for four to six months. These effects show the necessity for the strictest hæmatological control. Dr. Galton has carried out a most careful comparison of the responses to high and low dosage and as a result makes a plea, which I endorse, for the avoidance of higher doses. The drug is of no value in the acute leukæmias, or in acute relapse of the chronic leukæmias. Nevertheless it is of interest, within its severely limited application and in the most favourable cases, as having yielded substantially useful clinical results equal to or surpassing those provided by chemical agents in this or other forms of malignant disease.

According to Galton, if a new remedy is to compete successfully with radiotherapy it must be as efficacious and must be safe, free from undesirable side-effects, and easy to administer. An essential feature of radiotherapy is that it can induce remissions repeatedly, and in considering the claims of Myleran to a place in therapeutics he emphasized that little is yet known of its action on relapse following prolonged first remission. From what is beginning to be known, however, it appears the situation should be treated with considerable reserve, certain of such second responses having so far been less satisfactory, with in some cases minimal splenic regression, depression of platelets, and even acute relapse.

In the chemotherapeutic control of the reticuloses it seems to me improbable that any of the agents I have mentioned will find a permanent place. At the same time I should regard nothing more certain than that all these diseases will in time come under the influence of chemical agents immeasurably more powerful and specific than any we have at our command to-day. Firstly, there are indications from the most recent work that we have by no means sufficiently exploited the improvements to be expected on the basis of what is already known. Secondly, the more fundamental study of these various agents will almost certainly lead to advances of an altogether different kind, and thus render obsolete our present resources and ideas.

Dr. J. D. N. Nabarro: Nitrogen mustard has been shown to influence the course of Hodgkin's disease and other malignant lymphomata, and the indications for its use as a palliative agent in preference to deep X-rays are fairly well defined (Nabarro, 1949). If the lymphomatous process is well localized, deep X-ray therapy gives more complete and more prolonged remissions. In cases in which there is evidence of generalized disease, especially if associated with constitutional disturbances, for example fever and anorexia, chemotherapy should be considered. There are three difficulties in the use of nitrogen mustard. It has to be given intravenously, and unless the injection is made into the tubing of a fast running saline drip there is a high incidence of thrombosis. Secondly, about 70% of patients given the "bis" derivative, di-(2-chloroethyl)-methylamine hydrochloride—Mustine, get severe vomiting, and this is most distressing in patients already seriously ill. Thirdly, bone-marrow depression and fatal aplastic anæmia may follow its use.

After the introduction of nitrogen mustard, intensive studies were undertaken in many centres to find new derivatives that were equally effective and less liable to produce complications. One drug merits further trial, 2:4:6-triethylenimino-*s*-triazine, also known as triethylene melamine or T.E.M. This agent was discovered independently in this country (Rose *et al.*, 1950) and in the United States (Burchenal *et al.*, 1950). Early studies showed that it was therapeutically active and that it had certain advantages when compared to nitrogen mustard (Karnofsky *et al.*, 1951; Paterson and Boland, 1951). It can be given intravenously by direct injection without fear of venous thrombosis and furthermore is effective by mouth. It is much less likely to cause vomiting and this is never so severe as after nitrogen mustard. On the other hand bone-marrow depression and pancytopenia are readily induced.

Results

We started using T.E.M. at University College Hospital in August 1951 and we have records of 22 patients treated with the intravenous preparation and 26 by oral administration. Most of our cases were of Hodgkin's disease or other malignant lymphomata, many had had previous deep X-ray therapy, but were now considered on account of dissemination or constitutional disturbance more suitable for a trial of chemotherapy. A few had had no previous treatment but were thought after consultation with Dr. E. L. G. Hilton, the physician in charge of the Radiotherapy Department at the hospital, to be more likely to benefit from drug treatment. Many of the patients were referred by Dr. Hilton and her colleagues to whom my thanks are due.

The results of 29 courses given intravenously to 22 patients are shown in Table I, together with the criteria used for assessing the results; this is important because many reports have been over-enthusiastic in their evaluation of chemotherapeutic agents for malignant disease. The assessment is based on the patient's capacity for activity and work, and on the relief of distressing symptoms, but all patients who derived moderate or considerable benefit from the treatment also showed objective evidence of improvement. The results given in this Table are disappointing, but the dose used was rather small, and in this initial trial many advanced, often terminal cases were included. The 2 patients shown as obtaining considerable benefit had excellent remissions of nine months' duration.

TABLE I.—INTRAVENOUS T.E.M. THERAPY

Results obtained in 22 patients given 29 courses of 0·08–0·21 mg./kilo body weight—mean 0·14 mg./kilo

Disease	Number of patients	Considerable benefit	Moderate benefit	Transient symptomatic relief	Failure
Hodgkin's disease	9	1	0	3	5
Stem-cell lymphoma	1	0	0	0	1
Lymphoblastic lymphoma ..	2	0	0	0	2
Lymphocytic lymphoma ..	1	1	0	0	0
Clasmatocytic lymphoma ..	4	0	0	1	3
Unclassified lymphoma ..	2	0	0	0	2
Chronic myeloid leukæmia ..	1	0	0	1	0
Carcinoma of bronchus.. ..	2	0	0	1	1

Criteria of Assessment

Considerable benefit—able to return to their normal occupation for at least three months.
Moderate benefit—able to leave hospital and be about the home for at least three months.
Transient symptomatic relief—control of distressing symptoms or any remission lasting less than three months.

The results in 26 patients given oral T.E.M. which are shown in Table II are more encouraging, but in some cases treatment failed to influence the progress of the disease. A satisfactory response cannot be related to any clinical or histological picture, and it is impossible, without trial, to forecast what effect treatment will have in any particular patient. The 8 cases of Hodgkin's disease, shown as deriving considerable benefit, have been controlled by repeated courses for from three to six months,

TABLE II.—ORAL T.E.M. THERAPY

Results of treatment in 26 patients

Disease	Number of patients	Considerable benefit	Moderate benefit	Transient symptomatic relief	Failure	Too recent to assess
Hodgkin's disease	17	8	1	2	3	3
Clasmatocytic lymphoma..	1	0	0	1	0	0
Lymphoblastic lymphoma	3	1*	0	0	1	1
Lymphocytic lymphoma ..	1	0	0	0	0	1
Unclassified lymphoma ..	3	0	0	0	3	0
Carcinoma of bronchus ..	1	0	0	0	1	0

*Combined therapy of T.E.M. and cortisone, in a patient with a hæmolytic anæmia associated with lymphoblastic lymphoma.

and 5 are still responding well to the treatment. The length of remission following a single course has been from three to five months, but in 2 patients each given four courses of treatment it was noticeable that the remissions became progressively shorter and the hæmatological side effects more pronounced. [Slides were shown illustrating the effect of T.E.M. therapy on the fever, anæmia, splenomegaly and mediastinal lymphadenopathy of patients with Hodgkin's disease.]

Complications of T.E.M. Therapy

Intravenous therapy did not lead to venous thrombosis, and nausea and vomiting were minimal. The complications of oral therapy are shown in Table III. Nausea was common in patients given

Table III.—Complications of Oral T.E.M. Therapy

26 patients—49 courses—167 doses

Nausea: after 53% of doses
The incidence varied with the amount given—after 5 mg. 70%: after 3 mg. 28%.

Vomiting: after 4·7% of doses
Only occurred after doses of 5 mg. (Incidence 7·5%).

Possible *impairment of renal function:* 2 patients.

Hæmatological Complications:
After the initial course: Transient leucopenia: 1 patient.
Transient thrombocytopenia with purpura: 1 patient.
After prolonged treatment: Transient pancytopenia: 1 patient.
Persistent pancytopenia: 4 patients.

Leucopenia—W.B.C. <1,000 per c.mm.
Thrombocytopenia—Platelets < 50,000 per c.mm.
Pancytopenia—W.B.C. < 1,000: platelets < 50,000: reticulocytes < 0·1%.

the larger doses and continued for some days after the course was completed, vomiting was exceptional and never severe. Hæmatological complications were common, and persistent pancytopenia developed in 4 patients who received repeated courses of the drug.

Management of T.E.M. Therapy

Oral T.E.M. is an effective and easily administered form of palliative therapy for selected cases of malignant lymphoma. At the same time prolonged treatment has proved dangerous and unless a reasonably safe scheme of dosage can be evolved, the drug is unlikely to gain general acceptance. Three programmes have been suggested. One, which may be called "continuous therapy", consists of giving small doses at weekly intervals, each dose being preceded by a blood count. Remissions may be obtained in this way, but only after four or five weeks, and evidence of severe bone-marrow depression may suddenly appear after several months' treatment. We tried this method in a few cases, but gave it up after studying the American reports. The second programme may be called "intermittent therapy"; a short intensive course is given and only repeated when there is evidence of re-activation of the disease. A modification of this method involves re-treatment before there is re-activation—the so-called maintenance therapy. In most of our cases we have adopted the intermittent dosage programme without maintenance therapy.

The two important questions that have to be considered are the amount of T.E.M. that should be given in the initial course, and how soon treatment can safely be repeated. Dose should be based on the patient's body weight, and it seems from the results in our more successful cases that 0·25 mg./kg. body weight is usually an adequate therapeutic dose. On the other hand the bone-marrow of different individuals and in different diseases varies greatly in sensitivity. We have not had any persistent damage after the initial course, but it has been reported by others, and it is probably safer to give only 0·2 mg./kg. body weight in the first course. We use enteric-coated tablets[1] which give more consistent absorption (Paterson *et al.*, 1953). The course is given in divided doses on consecutive days and no single dose has exceeded 5 mg. If after ten days the white cell count has not fallen appreciably, the course was not the maximum the patient could tolerate and a further 0·07 mg./kg. should be given. When there is anything to suggest bone-marrow involvement, a leukæmic blood picture for example, the initial course should be considerably smaller.

The ease with which serious bone-marrow depression can be produced is the over-riding consideration in the planning of subsequent treatment. Persistent pancytopenia developed in 4 of our patients

[1] Supplies of T.E.M. used in this trial were provided by Imperial Chemical (Pharmaceuticals) Ltd.

and it is perhaps of value to examine their progress to see if any conclusions can be drawn about how to avoid this complication (Fig. 1). In the first 2 patients, although an appreciable fall in the white cell count followed the first course of treatment, the remissions were only transient and incomplete; despite this the drug was pushed in an attempt to secure a worth-while remission. The conclusion we drew from these two cases was that if after a course of T.E.M. sufficient to cause definite depression of the white cells, there is no reasonable remission, it is dangerous and useless to continue with its administration.

The third patient (Case 4 in Fig. 1) benefited considerably from his first two courses, his hæmoglobin rose from 68% to 98%, and a pleural effusion that had needed tapping every three days ceased to accumulate. The third course, however, led to depression of all the formed elements of the blood. ACTH and cortisone have been used for the treatment of bone-marrow depression after chemotherapy and through the courtesy of the Medical Research Council we have had a supply for trial in these patients. A course of ACTH (170 mg. by repeated prolonged intravenous infusions over twenty-four days) was given to this patient; his reticulocytes, white cells and platelets increased and, apart from some anæmia, his blood picture was normal when the course of ACTH was terminated. This may have been a natural recovery from the bone-marrow depression, or the effect of the ACTH. At the end of this course he was still febrile and had evidence of continuing activity of the lymphoma, a further course of T.E.M. was given and an attempt made to prevent the bone-marrow depression by simultaneous ACTH therapy. This was unsuccessful, pancytopenia developed and persisted until his death six months later. During this six months intensive treatment was given with ACTH, cortisone and blood transfusions, but it had little effect on his condition. He felt much better while on hormones and his period of survival was perhaps longer than one would have expected under the circumstances.

The fourth patient (Case 12 in Fig. 1) had an unusually severe and prolonged depression of blood cells and purpura after his first course. This is unusual in a case with recent onset and no previous treatment. The lymphoma responded well to the T.E.M. and when he relapsed three months later a

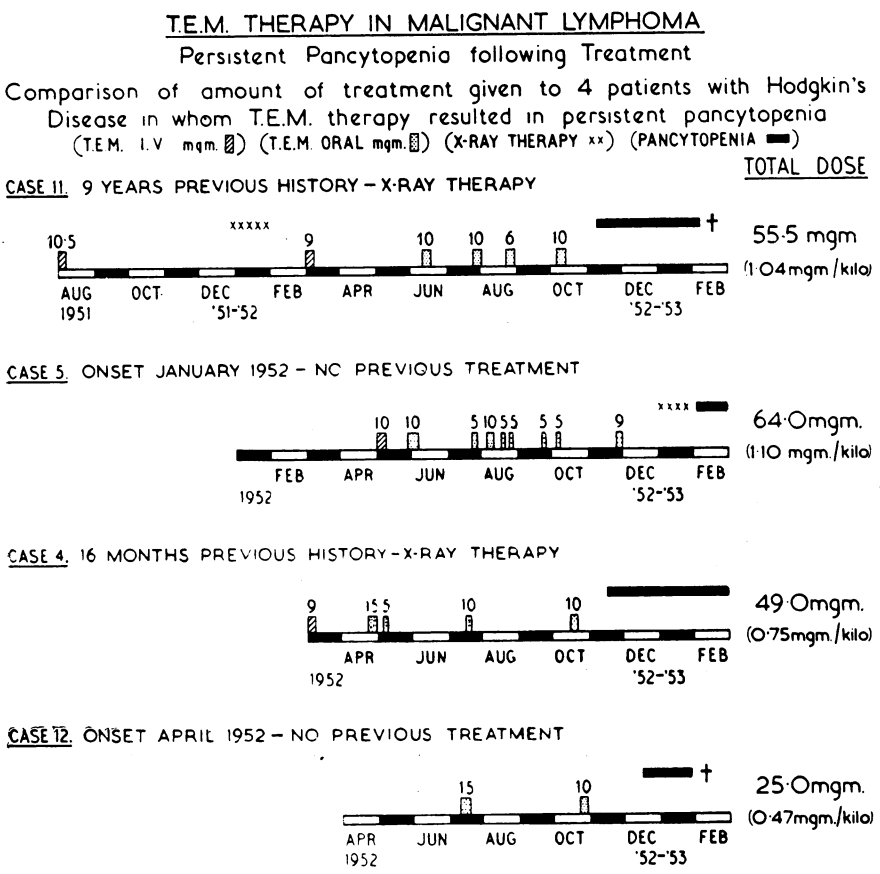

FIG. 1.

further course was given because no other form of treatment was considered practicable. This second course failed to influence his Pel-Ebstein fever and produced a persistent pancytopenia. ACTH had no effect on the lymphoma or the blood condition. It is perhaps significant that at autopsy the bone-marrow was heavily infiltrated with Hodgkin's tissue.

Conclusions

As the result of our experiences to date we have come to the following conclusions. Oral triethylene melamine is an effective palliative agent for patients with Hodgkin's disease. It is indicated in cases showing marked constitutional disturbance or wide dissemination of the disease. At the same time it is dangerous, readily producing aplasia of the bone-marrow and great care is needed in the planning of treatment. The initial course should not exceed 0·2 mg./kg. body weight, but if after ten days the white cell count shows little change a further 0·07 mg./kg. may be given. Smaller doses should be used in patients with any evidence of bone-marrow involvement. If there is evidence of unusual bone-marrow sensitivity following the first course, no more T.E.M. should be given. If the patient shows a definite fall of the white cell count, but only an incomplete and transient remission of the disease, further treatment with T.E.M. is contra-indicated. The drug should be given in definite courses as widely separated as possible, only in exceptional circumstances should a second course be given within two months of the first. There is some evidence that bone-marrow depression is more severe if several courses of treatment are given but further experience is required on this point.

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