of turning back to form orderly tissues. It has sometimes been thought that chromosome changes may be a late or secondary manifestation of neoplasia. The evidence from carcinoma-in-situ of the cervix uteri (Spriggs, Boddington, and Clarke, 1962) suggests, on the contrary, that the karyotype may be altered *before* the development of invasive cancer.

Our results therefore provide support for the view that in the common types of malignant tumour each growth consists of a population of cells with an altered genotype, derived from a common parent. Their biological success is due, presumably, to the natural selection of successful variants. The random element in this process accounts for the uniqueness of each malignant tumour and explains the failure to find any biochemical abnormality specific for malignant cells.

Summary

The chromosomes have been examined in dividing cells from human tumours. Most of the successful preparations were from malignant effusions, and counts are given from 17 of these as well as from two control serous fluids. Counts from five solid tumours are also presented—three primary and two secondary.

Malignant cells were found to have abnormal karyotypes, with a different pattern in each case. There is some variation of the chromosome number around an abnormal modal value, which is usually more than 46 but occasionally less. Secondary peaks are often found at multiples of the modal number.

When cells with a normal karyotype are present as well they are explained by the occurrence of dividing normal cells in the same specimen (as shown in stained smears).

In many of the tumour-cell populations it is possible to recognize distinctive abnormal chromosomes in all the cells, although their chromosome counts vary. This presumably indicates descent from the same original malignant cell.

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BIOCHEMICAL INVESTIGATION OF OUTBREAK OF INFECTIOUS HEPATITIS IN A CLOSED COMMUNITY

BY

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That elevations of serum glutamic oxaloacetic transaminase (S.G.O.T.) and serum glutamic pyruvic transaminase (S.G.P.T.) occur in infectious hepatitis was first shown by Wroblewski and La Due (1955, 1956b). Numerous reports, summarized in the valuable reviews by Wroblewski (1958) and Agress (1959), have since established the assay of these enzymes as a principal diagnostic measure in this disease.

It is clear that, during the course of an epidemic, anicteric forms of infectious hepatitis may exist widely among the population at risk (Denber and Leibowitz, 1952; Capps and Stokes, 1952). The problem of investigating such anicteric cases of infectious hepatitis has been facilitated by the introduction of serum enzyme tests, and Wroblewski and La Due (1956a) have made a notable contribution by their study of a naturally endemic form of the disease in a closed community at Letchworth Village, New York. Their results led them to classify those with only transiently abnormal S.G.O.T. as carriers; those with only abnormal S.G.O.T. and abnormal thymol turbidity as subclinical cases; and those with symptoms, abnormal S.G.O.T., and abnormal thymol turbidity in the absence of overt jaundice as subicteric cases.

These studies have been extended by Bodansky and his associates at the Willowbrook State School, New York (Ward, Krugman, Giles, Jacobs, and Bodansky, 1958; Bodansky, Krugman, Ward, Schwartz, Giles, and Jacobs, 1959; Krugman, Ward, Giles, Bodansky, and Jacobs, 1959). Their work on the naturally occurring and artificially induced forms of the disease represents impressive evidence for the superiority of serum transaminase estimations over every other laboratory parameter in the detection of latent and subclinical cases, while their transmission experiments have confirmed the long period of infectivity which may precede the onset of icterus—up to three weeks—as well as the potential infectivity of otherwise healthy and symptomless carriers described by earlier workers (Paul, Havens, Sabin, and Philip, 1945; Havens, 1946a, 1946b; Francis, Frisch, and Quilligan, 1946).

More recently, serum enzyme studies, including assay of S.G.O.T. and S.G.P.T., were applied to an outbreak of infectious hepatitis in Poppenlauer, West Germany (Schön and Wüst, 1961), in which the disease took an anicteric form in 70% of the cases. The authors concluded that the measurement of S.G.P.T. was the most sensitive test available for diagnostic and epidemiological purposes.

The opportunity arose for a study of subclinical cases of infectious hepatitis in a ship from India berthed in Glasgow, with a total crew of 236. This study was undertaken as a result of two members of the catering

crew presenting at this hospital with classical icteric infectious hepatitis. The conditions aboard ship were such as to enable the crew to be classified as a closed community, and before permitting passengers aboard it was felt desirable to assess the extent of the infection and to take such preventive measures as were possible and appropriate.

Methods and Scope of Investigation

Every member of the crew who had completed the journey from India had blood withdrawn for analysis. For the purpose of this first analysis, the crew was divided into two sections and the examination of each section took place independently, the interval between these examinations being 10 days.

The entire catering staff and some European members of the crew were sampled over a two-day period, July 24-25, while the ship was in Glasgow, and S.G.P.T. activity was estimated by the method of Wroblewski and Cabaud (1957). Specimens which yielded a result of less than 50 units/ml. were not examined further. Where the result equalled or exceeded this value, other investigations were carried out. These comprised in rough order of preference thymol turbidity and thymol flocculation tests (MacLagan, 1944; Neefe, 1946), zinc sulphate turbidity test (Kunkel, 1947), bilirubin (Malloy and Evelyn, 1937), S.G.O.T. (Cabaud, Leeper, and Wroblewski, 1956), and alkaline phosphatase (King, Haslewood, Delory, and Beall, 1942). Four days after this initial phase of the investigation, when the ship was in Liverpool, those members whose S.G.P.T. activity had been 50 or more units/ml. were re-examined biochemically.

A week later blood from the remainder of the crew was withdrawn in Liverpool and transported immediately to this department, where the procedures previously mentioned were carried out. Three weeks later, when the ship had reached Bombay, further specimens were taken by the ship surgeon from those crew members whose S.G.P.T. activity on August 4 had been 50 or more units/ml., the serum being separated and frozen. Analyses were carried out on these specimens when the ship returned to Glasgow, and fresh specimens were taken from all crew members then available whose S.G.P.T. activity at the second or subsequent sampling had not returned to a value lower than 50 units/ml.

Results and Discussion

In accordance with standards established for this department, it was decided to regard as abnormal an activity of 50 or more units/ml. for both serum transaminases; a serum bilirubin exceeding 1.2 mg./100 ml.; serum thymol turbidity greater than 3 units and flocculation of whatever degree; zinc sulphate turbidity above 14 units; and serum alkaline phosphatase activity in excess of 13 units/100 ml.

Examination of First Section.—Of the 126 members examined during the first two-day period, 89 had normal S.G.P.T. activity as defined above (these normal results are presented in Fig. 1), 21 had S.G.P.T. activity of 50-69 units/ml., and 16, including the two original jaundiced cases, had S.G.P.T. activity of 70 or more units/ml.

Examination of Second Section.—Of the 93 members examined for the first time 10 days later, 87 had normal S.G.P.T. activity (these results are presented in Fig. 1),

4 had S.G.P.T. activity of 50-69 units/ml., and 2 had S.G.P.T. activity in excess of 70 units/ml.

For the purpose of presenting all the data available on the cases subjected to a further examination, those with an initial S.G.P.T. activity of 70 or more units/ml. have been grouped together and those with an activity of 50-69 units/ml. have been grouped together (Table I).

FIG. 1.—Distribution of S.G.P.T. activity in members of crew regarded as normal at initial examination.

Serial Results of Cases with High S.G.P.T. Activity

It will readily be seen that, of these cases (Table I, Cases 1-18), the S.G.P.T. activity had fallen on the second sampling in all but one person (Case 4). Except for Case 15, this fall was considerable, in nine persons being to within the normal limit. At the time of the final examination the S.G.P.T. activity of all but one of the cases examined had returned to normal, but three seamen in this group had changed ship and could not be further investigated.

Fifteen of these first 18 cases had, in one or other of the first two specimens, biochemical derangement suggestive of liver damage. Of these, seven had abnormalities of serum turbidity tests and hyperbilirubinaemia; four had hyperbilirubinaemia with normal turbidity tests; and four had abnormal turbidity tests with normal serum bilirubin. Three of the 18 cases do not have data supporting liver damage apart from raised S.G.P.T. activity. Of these, one had no other investigations carried out on the first specimen, and the second specimen showed normal S.G.P.T. activity (Case 9). From the "status" column, as well as from the individual results, it can be seen that the general tendency is towards improvement in the ancillary tests with later samples; but this is by no means invariable, some specimens showing improvement in one index and deterioration in another, while the overall picture is blurred by the impossibility of obtaining complete data in the circumstances.

The S.G.O.T. results were used to compare the sensitivity of this enzyme activity with that of S.G.P.T. as a screening procedure. In none of the 18 cases did S.G.O.T. activity exceed S.G.P.T. activity at the initial examination. The higher values for the latter were striking in most patients; and indeed five, in four of whom there was good evidence of hepatic impairment

from ancillary tests, would have been classified as normal if S.G.O.T. activity had been used as the only screening procedure.

Symptoms of clinical signs were present in only the first 10 cases and were distributed as follows: fever (5 cases), nausea and vomiting (5 cases), transient hepatomegaly (4 cases), icterus (5 cases), bile and/or excess urobilinogen in the urine (5 cases).

In view of the frequent association of other biochemical abnormalities indicative of disturbed hepatic function in this group and in the presence of two classical cases of infectious hepatitis, one is led to the conclusion that the raised S.G.P.T. activities were a manifestation of acute liver damage, which in all but one case (No. 4) was subsiding at the time of examination. This conviction is strengthened by the relationship between S.G.P.T. and S.G.O.T. activities which militates against the possibility of chronic liver or cardiac damage (Wroblewski and La Due, 1956b; Chinsky, Wolff, and Sherry, 1957; De Ritis, Coltorti, and Giusti, 1957). That alkaline phosphatase determinations, where carried out, do not support biliary obstruction as a cause of raised serum transaminase activities lends further credibility to this view. Drugs,

TABLE I.—Biochemical Data

Case No.	1961 Date	S.G.P.T. (Units/ml.)	S.G.O.T. (Units/ml.)	Bilirubin (mg./100 ml.)	Alkaline Phosphatase (Units/100 ml.)	Thymol Turbidity (Units)	Thymol Flocculation (Units)	Zinc Sulphate Turbidity (Units)	Status*
<i>Cases showing S.G.P.T. Activity of 70 or More Units/ml.</i>									
1	21/7	1,120	—	13.4	—	6	4	—	BTFZ
	25/7	750	—	5.7	12	4	3	—	BTFZ
	28/7	176	50	3.5	—	4	2	14	BTFZO
2	21/7	1,120	210	6.9	19	6	2	26	BTFZO
	28/7	88	—	2.4	—	4	1	11	BTF
3	25/7	850	700	2.5	—	4	1	10	BTFO
	28/7	776	—	2.9	—	5	0	13	BT
	4/8	170	28	1.5	—	4	3	12	BTF
	25/8	20	—	—	—	3	1	11	F
4	25/7	538	—	0.8	9	1	0	4	N
	28/7	760	150	1.3	—	2	0	7	BO
	4/8	290	90	0.8	—	2	0	6	O
	17/10	29	31	—	—	—	—	—	—
5	24/7	312	104	4.7	15	4	1	12	BTFO
	28/7	112	62	0.4	9	4	1	13	TFO
	17/10	36	36	—	—	2	0	12	—
6	25/7	274	120	2.0	8	2	0	5	BO
	28/7	72	—	1.0	—	2	0	5	N
7	25/7	150	65	0.5	—	2	0	7	O
	28/7	55	11	0.1	—	3	0	12	O
	17/10	136	55	0.8	10	1	0	10	O
8	25/7	115	55	0.5	12	5	2	11	TFO
	28/7	50	38	0.7	—	2	0	8	N
	17/10	26	—	—	12	3	0	15	Z
9	24/7	100	—	—	—	—	—	—	—
	28/7	26	—	0.5	—	3	0	11	N
10	24/7	94	75	2.9	6	4	1	18	BTFZO
	28/7	24	—	3.3	—	4	1	16	BTFZ
11	25/7	92	14	0.4	—	5	2	14	TF
	28/7	43	—	0.3	—	4	0	12	T
	17/10	44	—	—	—	3	0	17	Z
12	24/7	85	29	—	10	3	0	10	I
	28/7	35	—	1.0	—	3	0	15	Z
13	25/7	85	63	0.4	—	3	0	7	O
	28/7	48	—	1.5	—	3	0	12	B
14	24/7	82	47	—	—	2	0	10	I
	28/7	18	—	1.8	—	3	0	12	B
	17/10	28	—	0.2	—	2	0	8	—
15	25/7	75	50	1.5	—	3	0	12	BO
	28/7	72	25	0.5	—	3	1	13	F
	17/10	22	—	—	—	2	0	13	—
16	24/7	70	12	2.2	6	3	1	17	BFZ
	28/7	14	—	1.0	—	3	0	16	Z
17	4/8	75	—	1.0	7	3	1	10	F
	25/8	25	—	—	—	2	0	9	—
18	4/8	84	40	0.7	—	1	0	3	N
	25/8	37	—	—	—	—	—	—	—

TABLE I—continued									
Case No.	1961 Date	S.G.P.T. (Units/ml.)	S.G.O.T. (Units/ml.)	Bilirubin (mg./100 ml.)	Alkaline Phosphatase (Units/100 ml.)	Thymol Turbidity (Units)	Thymol Flocculation (Units)	Zinc Sulphate Turbidity (Units)	Status*
<i>Cases showing S.G.P.T. Activity of 50–69 Units/ml.</i>									
19	24/7	68	60	0.2	8	3	0	13	O
	28/7	75	25	—	—	5	0	13	T
	17/10	40	—	—	—	4	0	10	T
20	25/7	66	29	0.9	—	2	0	9	N
	4/8	14	—	—	—	—	—	—	—
21	24/7	65	22	0.3	8	2	0	11	N
	28/7	15	—	—	—	2	0	8	—
22	24/7	65	31	1.5	8	3	0	15	BZ
	28/7	65	—	—	—	3	0	15	N
	17/10	26	—	0.2	—	3	0	15	Z
23	24/7	64	47	0.9	8	1	0	10	N
	28/7	14	—	—	—	—	—	—	—
24	24/7	64	20	2.0	11	3	0	11	B
	28/7	58	—	—	—	—	—	—	—
	17/10	26	—	0.8	—	2	0	11	N
25	25/7	64	60	0.4	12	10	4	25	TFZO
	4/8	14	3	—	—	5	2	20	TFZ
26	25/7	64	30	0.1	6	3	0	11	N
	4/8	15	—	—	—	—	—	—	—
27	25/7	64	29	—	—	—	—	—	I
	4/8	44	—	—	—	—	—	—	—
	17/10	42	—	—	—	—	—	—	—
28	25/7	64	60	0.5	11	12	2	13	TFO
	4/8	11	24	—	—	9	1	9	TF
29	24/7	62	—	—	—	—	—	—	—
	28/7	62	—	—	—	—	—	—	—
	17/10	58	20	0.2	5	1	0	15	Z
30	24/7	59	42	0.2	9	3	0	13	N
	28/7	34	—	—	—	2	0	12	—
31	24/7	58	29	1.5	11	3	0	16	BZ
	28/7	16	—	0.9	—	2	0	11	N
32	25/7	58	—	0.8	8	2	0	9	N
	4/8	12	—	—	—	—	—	—	—
33	25/7	56	—	—	—	—	—	—	I
	4/8	2	—	—	—	—	—	—	—
34	25/7	55	—	—	—	—	—	—	I
	4/8	12	—	—	—	—	—	—	—
35	25/7	55	—	—	—	—	—	—	I
	4/8	0	—	—	—	—	—	—	—
36	25/7	55	—	—	—	—	—	—	I
	4/8	14	—	—	—	—	—	—	—
37	25/7	54	—	—	—	—	—	—	I
	4/8	18	—	—	—	—	—	—	—
38	25/7	52	—	—	—	—	—	—	I
	4/8	2	—	—	—	—	—	—	—
39	25/7	52	—	—	—	—	—	—	I
	4/8	34	—	—	—	—	—	—	—
40	4/8	62	40	1.6	—	1	0	12	B
	25/8	25	—	—	—	1	0	10	I
41	4/8	61	30	1.5	8	3	0	10	B
	25/8	16	—	0.5	—	—	—	—	—
42	4/8	60	25	1.7	6	2	0	7	B
	25/8	31	—	0.7	—	—	—	—	—
43	4/8	50	25	0.7	—	—	—	—	I
	25/8	13	—	—	—	—	—	—	—

* Abnormalities of bilirubin, thymol turbidity, thymol flocculation, zinc sulphate turbidity, and S.G.O.T. are indicated by symbols B, T, F, Z, and O respectively. Where a complete set of results is normal, this is indicated by symbol N. Where the data are incomplete, this is denoted by symbol I.

injections, and hepatic poisons were excluded as possible causes.

Serial Results of Cases with Moderately Elevated S.G.P.T. Activity

Analysis of the data in Table I shows that, of 25 cases in which the initial S.G.P.T. activity was 50–69 units/ml., all but four had normal activity at the second examination; three of these four subsequently returned to normal at the final examination.

Ancillary investigations were carried out on fewer of these cases than on those with high S.G.P.T. activity. Of the 25 cases, 9 provide no further evidence on the question of hepatic dysfunction. Of the remaining 16

to whom a status could be allotted, 6 fall quite definitely into the category of those showing no abnormality other than that of raised S.G.P.T. activity. Two cases show abnormalities of serum turbidity tests as well as hyperbilirubinaemia, while four show abnormal serum turbidity tests alone, and another four hyperbilirubinaemia alone. Once again the results show consistently higher activities of S.G.P.T. than of S.G.O.T., the latter being raised in only 3 of the 17 cases where both were assayed; and of the 14 cases with normal S.G.O.T. activity the ancillary tests showed some abnormality in seven, conclusively no abnormality in five, and no status could be defined for the remaining two. No elevation of serum alkaline phosphatase activity was detected in the specimens examined; and the general trend towards status improvement with successive samples emerges on detailed analysis.

Once again the data available make it appear that the most likely cause of such S.G.P.T. elevation, in at least a high proportion of this group, lay in transient liver damage presumably due to the virus of infectious hepatitis. The severity of this infection is impossible to define, but when one assesses the rapidity with which all biochemical indices improved in Cases 1 and 2 one is forced to concede the possibility that several cases with S.G.P.T. activity of 50–69 units/ml. are in the recovery phase of subclinical forms of the disease.

Cases with Normal S.G.P.T. Activity

The mean S.G.P.T. activity (25.6 units) of those members of the first section in whom the initial value fell below 50 units/ml. was higher than the corresponding mean (19.4 units) for the second section (see Fig. 1). The standard error of the mean for the two groups is identical (4.32) and the difference in the means is statistically significant. Transportation of the specimens is unlikely as a cause of this difference in view of the well-established stability of serum transaminases (Wroblewski, 1958), and the fact that delay in separating serum from cells tends to elevate activity (Bang, Reugsegger, Ley, and La Due, 1959). Further analysis, interchanging the values for S.G.P.T. activity below 10 units/ml., produced means which still differed significantly, whereas on interchanging the values above 30 units/ml. the difference became negligible, leading to the conclusion that the population examined on July 24 and 25 had a preponderance of individuals with high normal S.G.P.T. activity. This raises the possibility that certain of these may have been recovering from transient subclinical infectious hepatitis, and had the crew been examined earlier many more abnormal cases might have come to light.

Further Technical Considerations

The stability of the other properties of serum examined in this investigation under the conditions employed has been established in this department. Where possible, abnormal results were confirmed by repetition of the analysis. Although the criteria adopted for interpretation of thymol turbidity and thymol flocculation tests are not universally accepted, they were first put forward by Neefe (Neefe, 1946; Neefe and Reinhold, 1946), supported by Mateer, Baltz, Comanduras, Steele, and Brouwen (1947), and accepted with reservations by MacLagan (1947), who demonstrated that hepatitis gamma-globulin alone among the fractions of sera tested will flocculate in thymol buffer (MacLagan and Bunn, 1947).

Epidemiology

Analysis of the cabin distribution of members of the catering crew sampled during the two days of the investigation (Table II) shows that cases are distributed

TABLE II.—Cabin Distribution of Abnormal Cases: Catering Crew

Cabin No.	No. of Occupants	S.G.P.T. Activity 70 or More Units/ ml. No. of Cases	S.G.P.T. Activity 50–69 Units/ml. No. of Cases
1	12	2	2
2	13	5	1
3	18	1	4
4	14	3	4
5	4	1	0
6	14	1	2
7	2	1	1
8	16	0	3
9	1	0	0
10	3	0	1
11	5	0	2
12	1	0	0
13	1	0	0
14	16	1	2
15	1	1	0
16	1	0	1

among cabins in a random manner. This, together with the almost uniform stage of the infection in every case, supports the known gastro-intestinal transmission of the disease.

The age distribution of the total crew* is presented in Fig. 2, together with the number of cases within each decade showing abnormalities of S.G.P.T. activity at the initial examination. The apparent maximal incidence in the decade 40–49 is in line with the findings of Schön and Wüst (1961) but a little earlier than the peak

Fig. 2.—Age distribution of total crew and cases with abnormal S.G.P.T. activity.

incidence in the adult cases of Ward *et al.* (1958). As chronic liver disease ought empirically to occur more often in the older age-groups, the claim to regard those with S.G.P.T. activity of 70 or more units/ml. as probably recovering from infectious hepatitis is strengthened by the fact that no person over 60 years fell into this category.

The biochemical findings in this outbreak differ in certain respects from those previously reported, which in turn show variation among themselves. For example, Wroblewski, Jervis, and La Due (1956) speak of a gradual rise and fall of both serum transaminases in

*Age could be traced in only 229 members of the crew, and of this number only 219 were available for examination.

the Letchworth Village infection, while Bodansky *et al.* (1959) describe a crescendo-like rise and fall in the Willowbrook patients. The Poppenlauer epidemic (Schön and Wüst, 1961) differed from both of these in the respect that in no case did elevated activity of serum transaminases precede clinical symptoms. It seems possible that, in view of the isolation of several virus strains from cases of infectious hepatitis capable of propagating the disease (Rightsel, Keltsch, Taylor, Boggs, and McLean, 1961; Boggs, Capps, Weiss, and McLean, 1961), infection with a particular strain may result in a biochemical pattern differing from that produced by other strains.

Conclusions

The above investigation suggests that the S.G.P.T. activity is the most reliable index of infectivity during an outbreak of infectious hepatitis in a closed community, and offers the widest knowledge of the extent of all forms of the disease. It is recommended that, where it becomes necessary to screen a population, all members showing activity of 50 or more units/ml. should have the test repeated after an interval of about seven days. If the activity has fallen considerably it is reasonable to assume that the patient is not infectious after 10 days from the initial examination. If the activity is rising, then the patient is infectious. If it is static, or shows only minor changes, the possibility of chronic liver damage or biliary obstruction should be considered, and other tests of liver function undertaken in order to define the status of the individual more precisely. While such steps need hardly be taken with sporadic cases, they may be desirable during an infection of epidemic proportions. However, a thorough search for contacts and carriers among those concerned in the food industry may be desirable when even sporadic cases arise, and the above protocol might apply equally well under these circumstances.

Summary

An outbreak of infectious hepatitis among a ship's crew was investigated using assay of S.G.P.T. as a procedure for selecting those cases thought worthy of further examination.

Out of a total crew of 236, 18 had initial S.G.P.T. activity of 70 or more units/ml. The results of serial repetition of this assay, the clinical findings, and evidence from conventional tests of liver function support the conclusion that most, if not all, of this group were recovering from infectious hepatitis, which in all except two cases would have escaped diagnosis.

A further 25 had initial S.G.P.T. activity of 50–69 units/ml. The investigations were less complete than in the preceding group, but data from serial enzyme assays and liver-function tests make it appear probable that a high proportion were recovering from subclinical forms of infectious hepatitis.

The pattern of results supports the known gastro-intestinal transmission of this disease, and suggests that all those affected contracted the infection at or about the same time.

The superiority of the S.G.P.T. assay over that of S.G.O.T. is clearly shown, and it is suggested that where it becomes necessary to screen a population for carriers or subclinical cases of infectious hepatitis, a value of 50 units or more for the S.G.P.T. assay should be

regarded as an indication of infection until proved otherwise.

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The Minister of Health, Mr. Enoch Powell, opened a new training centre for subnormal children and a new ambulance depot at Warwick on November 9. He said that every week, somewhere in Britain, a new training centre for the mentally subnormal was being opened; every fortnight, somewhere in Britain, at least one new ambulance station was being brought into use. This showed the impetus with which the health and welfare services of all kinds were now expanding and moving forward. Mr. Powell emphasized that training centres such as these, if they were to do their work properly, must be located at the heart of the community they served, no less than if they were schools in the ordinary sense. For subnormal children they took the place of school, and their acceptance in the general community was an essential part of that great movement of practice and opinion which was transforming the outlook for the mentally handicapped. In the last decade the number of ambulances in service had increased by 25%, and even more significant had been the increase in efficiency resulting from the general adoption of radio control and the continuous improvement of equipment, both mobile and static.