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LATE RESULTS OF OPERATIONS FOR FALLOT'S TETRALOGY

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Fallot's tetralogy is the most common form of morbus caeruleus: its frequency was mentioned by Peacock in his excellent account in 1866. Its surgical treatment is therefore of great importance, and three methods are now available: (1) subclavian-pulmonary anastomosis or some modification of this; (2) Brock's direct operations of pulmonary valvotomy or infundibular resection or both; and, more recently, (3) open operation with closure of the ventricular septal defect and relief of the stenosis.

This paper describes the results of the first two methods, but I am able to mention my first patient, on whom Sir Russell Brock used the third method in October, 1956. A girl who was aged 4 at the time of her operation, and who was deeply cyanosed and could walk only 30 yards, is now acyanotic and can run about freely with other children, so that symptomatically she could hardly be better. The result, however, is not ideal, for, though her ventricular septal defect seems to have been closed, she still has some stenosis, with a larger heart and right bundle-branch block.

Clearly this third method is the only cure, and will become standard treatment when the present difficulties have been surmounted. The results of anastomotic operations may then be mainly of historic interest, but will serve as a comparison with the results of open operation after another ten years. Valvotomy and infundibular resection will, of course, remain an essential part of any surgical treatment, so that the success they can achieve is of great interest.

Inevitably, as time passes, the child who has had a successful operation for Fallot's tetralogy tends to be compared with the normal child of his age and less with the severely disabled child he was, both by the patient and his parents and by the physician as well. To this extent there is less enthusiasm than at first, and sometimes it needs to be remembered how many patients are leading normal quiet lives at school or at work who previously had no such prospect. This change of attitude is even more important when the patient was only somewhat improved; parents who were delighted at first think mainly of the great disability that remains after a few years.

ANASTOMOTIC OPERATIONS

All types of morbus caeruleus were included in our previous report of the results of 200 anastomotic operations (Campbell and Deuchar, 1953). This makes the conclusions less precise and less easy to follow, so here we are considering only those diagnosed as Fallot's tetra-

logy: this still includes some where necropsy revealed more complex lesions, but it excludes those with pulmonary atresia or tricuspid atresia where the results are not so good.

After this modification there are 130 patients who obtained good or very good results—127 from the start and 3 from later who were originally classed as "improved" only (see Table I). Those in whom the results

TABLE I.—Early Results of Anastomotic Operations

	No.	Died at Operation	No Op. Possible	No Improvement	Slight Improvement	Good	Very Good
Fallot's tetralogy ..	165	14	4	5	15-3*	33+3	94
Pulmonary atresia ..	19	6	5	0	3	3	2
Other conditions ..	16	4	2	1	1	3	5
	200	24	11	6	19	39	101

* Three of these subsequently achieved good results, making 130 (94+33+3) whose further progress is considered.

of operation were good and those in whom they were very good have behaved in much the same way, and it is simpler to take them together.

During the period covered in our previous report, up to four years after operation, few of the patients with good results had relapsed. During the subsequent four years we became less satisfied, for several returned to hospital having lost all their improvement. A further follow-up has been more reassuring, for we had seen nearly all those who were doing badly but few of those who were doing well, as they had felt no need to attend hospital.

Of the 130 who obtained good results, we have seen 126 recently or have had reports from them or their doctors. Eight of these (6%) have died and 17 (14%) have lost much or all of their improvement, but 101 (80%) are as good or nearly as good as they were. These have been followed for an average period of over seven and a half years: 11 are well after ten years, 10 after nine years, 28 after eight years, 36 after seven years, and 16 after six years.

Good Results Maintained

Most of these 101 patients have kept all their improvement, though seven have lost some of it—enough for the results to be called good rather than very good. The first 10 patients, most of whom were very disabled before operation (Campbell, 1948), have their cases described briefly to illustrate the results, which were very good in the first five but more varied in the second five. None of them, except Case A5, has an unduly large heart, and all show less

anoxaemia and lower haemoglobin percentages (see Table II), the average of the first five being 104 instead of 136%, though generally they are still a little cyanotic. It is only fair to add that Mr. Alfred Blalock was working at Guy's Hospital and performed some of these first operations, lest others feel that their start was not so successful. The

TABLE II.—Changes in Heart Size and Haemoglobin Percentage in Patients Who Have Done Well for 9 or 10 Years After Anastomotic Operations

Case No.	Heart Size (Cardiothoracic Ratio)						Haemoglobin (%)		
	Before Op.	1 Yr.	3 Yr.	5 Yr.	7 Yr.	9 or 10 Yr.	Before Op.	After 4 Yr.	After 9 or 10 Yr.
A1	50	53	53	54	55	55	126	91	110
A2	44	52	53	53	54	53	120	95	98
A3	51	55	55	54	53	52	133	85	114
A4	44	56	55	53	54	54	152	84	103
A5	52	60	65	67	66	65	150	80	95
A13	45	47	48	49	49	50	150	120	122
A16*	52	53	53	52	53	52	130	90	98
A20	47	52	53	53	53	50	110	100	105
A23*	43	48	48	49	50	51	130	85	95
A24	45	53	53	52	52	51	148	95	105
Average	47.3	52.9	53.6	53.6	53.9	53.3	135	93	104
Average of 50 cases	49.8	—	53.9	—	—	53.7	132	104	111
Some More Borderline Cases									
A62	51	51	51	51	48	46	152	110	132
A55	56	55	56	55	55	55	141	120	134
A83	54	59	59	58	57	54	136	127	150

A=anastomosis.

* These two patients were in good health after 9 years but died in the tenth year from cerebral abscess.

ages given are those at the time of operation unless otherwise stated. The prefix "A" indicates anastomotic operations.

Case A1.—A boy aged 7 was enabled to lead a normal life at school except for games. After ten years he can walk five miles and get about his father's farm most of the day, but would find it difficult to earn his living on a farm and is still a little cyanotic.

Case A2.—A boy aged 13; now leads a normal quiet life and is married. For two years he worked long hours in a garage but found this hard, and is now in an accountant's office. His colour looks normal.

Case A3.—A boy aged 3; is now leading a normal school life, except for football. He can walk five miles and can run and play cricket. He has minimal cyanosis.

Case A4.—A boy aged 11 could not walk more than 50 yards, but now walks 10 to 15 miles and his colour is almost normal.

Case A5.—A girl aged 6 could not walk more than 25 yards.

After ten years she attends school regularly but has to take things at her own pace. The heart became much larger, but not progressively so.

Case A6.—A girl aged 3 lost her improvement when the anastomosis closed in the seventh year (see below).

Case A7.—A boy aged 7 was very well when his family emigrated to Canada after two years.

Case A8.—A student aged 25 was less disabled than most. He has done well as regards his heart, but has been handicapped by the effects of a cerebral thrombosis after operation and by tuberculosis of the lungs.

Case A9.—A girl aged 5 was greatly improved and the operation probably saved her life, but four years later she was still disabled enough to need a second operation.

Case A10.—A boy aged 3 has continued to do well. In the tenth year he had bacterial endocarditis, but has not lost any ground after it.

Most of these patients were children, who on the whole do best after operation, but some adults do very well. Generally, if patients over 20 can earn their living the obstruction to the pulmonary flow cannot be great, and I have thought it better for them to carry on without operation. However, one man aged 20 who had never worked is now employed regularly as a painter and decorator, and can walk as far as he wants; another, aged 26, is so much better that he sometimes plays football in addition to doing his regular work; both have remained well for six years.

Some patients included among the good results are not as good as the best of these. They cannot do so much and show obvious cyanosis: a doctor seeing them for the first time would diagnose Fallot's tetralogy and might think they needed surgical treatment. Of three such patients, the first is not as well as he was and the other two are still examples of fairly severe Fallot's tetralogy (see bottom of Table II), but it is difficult not to call the results good when two who could not walk 50 yards before operation can now earn a living and the third can attend an ordinary school and walk much further than before.

Case A62.—A boy aged 6 lost some of his improvement after six years and the haemoglobin rose again; but after nine years he is earning his living and can walk a quarter of a mile, instead of 50 yards before operation.

Case A55.—A boy aged 11 was deeply cyanosed and could walk only 50 yards. Nine years later he is doing clerical work and can walk two miles, although his haemoglobin has risen again. He would be better if he had a larger blood flow to the lungs, but his heart might not be able to cope with this, as it has always been rather large.

Case A83.—A girl aged 6 had severe cyanotic attacks and could walk only 400 yards. After operation she could walk two

FIG. 1.—Exceptional enlargement of a small heart of a patient with Fallot's tetralogy. Left: Before operation (c.t.r. 48%). Centre: One year after operation, a larger heart (c.t.r. 57%), with lung fields that are much better filled. Right: Nine years after with a very large heart (c.t.r. 70%). She was then well, but died later that year with congestive heart failure. Slight rib-notching can be seen on the fifth right rib from the anastomotic channels from the aorta to the right arm after division of her right subclavian artery and, in retrospect, very slightly even in the radiograph one year after operation. Case A25.

miles and attend an ordinary school, but her colour and her haemoglobin did not improve much. After nine years she is almost as well, but is less contented because she cannot keep up with her friends.

Some patients who obtained a good result as regards their heart are handicapped in other ways. For example, one has some residual disability from post-operative cerebral thrombosis, another from a cerebral abscess, and a third from bronchiectasis. Two are dissatisfied because they are unable to work since leaving school, but this is because they are not intelligent enough to overcome their lack of schooling, and not because the heart has become worse.

Many of the patients are better in summer and can do much less on cold days in winter. Apart from this, any suspicion of deterioration has generally been confirmed by the subsequent course. However, two patients who were thought to be losing ground in the third and fourth years—a period of rapid growth—are as well as ever after seven years.

Good Results Lost

These patients have been divided into three groups: (a) those who have died, (b) those who have lost all their improvement, and (c) those who have lost much of it. The loss is not always due to the anastomosis closing.

Eight Patients Who Have Died

In our earlier report three had died (the fourth included there had tricuspid atresia). When we started this longer follow-up only two more had died, but during the tenth year three who were in excellent health after nine years have died. This may be chance, but shows the need for a long follow-up to get a reliable picture.

Of the three first, a woman aged 20 died suddenly in the street 18 months after operation, no obvious cause being found at necropsy; a girl aged 7 died unexpectedly from pulmonary oedema while on holiday 37 months after operation; and a boy aged 3 died with a cerebral abscess in the third year after.

Of the next two, a boy aged 11 remained well until he had acute nephritis in the sixth year; he recovered, and his blood pressure, which had risen to 170/130, returned to 120/90 mm., but five months later he died at home, probably from a recurrence of the nephritis. Our oldest patient, aged 35, did well for seven years, but then died with carcinoma of the bronchus.

The last three are particularly disappointing, for they had been leading active lives with few symptoms, and when examined nine years after their operation only one had signs that caused any anxiety—anaemia and a large heart; yet they died within a year. Two of them, boys aged 6 and 19, died from cerebral abscesses, both in the tenth year (Cases A16 and A23): the latter had made a good recovery after operation for a cerebral abscess at a different site seven years previously. The last, a girl aged 6, did very well, but her heart became much larger than usual (c.t.r. 47–60%). After nine years it was still larger (Fig. 1), but we hoped part of this was due to her anaemia (haemoglobin 71%) and might be reversed by

treatment. Nine months later, however, she was admitted with sudden severe dyspnoea, congestive failure, and anaemia: she seemed to be recovering, but became more breathless and vomited, and died suddenly a few hours later. At necropsy the immediate cause was a mesenteric thrombosis, but she should be regarded as dying from heart failure (Case A25).

Rather surprisingly, none of these patients showed any cardiac deterioration until their terminal illness; we have no reason to think that the anastomosis had closed, and have necropsy proof that it was open in five of the eight. One death from carcinoma of the bronchus was quite incidental and one from nephritis may or may not have been, for we find nephritis rather common in these patients; three were from cerebral abscess; and only three from some form of heart failure.

As the average period of follow-up for all our patients is over seven years, this is a mortality of about 1% per annum. In those who have died the average period after operation was just over three years in four and just under nine years in four.

Loss of All Improvement

Ten other patients have lost all their improvement. When the loss has taken place fairly suddenly—though sometimes in more than one stage—and the continuous murmur can no longer be heard, the reason is clear and in several operation or necropsy confirmed that the anastomosis had closed. This happened in the first five patients shown in Table III, and they reverted to the same state as before operation.

When the loss is gradual it is more difficult to explain in this way, and Case 45 was becoming worse for four years before there was any noticeable change in the continuous murmur: it seems that the stenosis was becoming more severe and that only towards the end was the anastomosis nearly closed. In the last four patients, however, the continuous murmur could be heard as well as before: we think they were showing the natural tendency for the stenosis of Fallot's tetralogy to become more severe, though in some the anastomosis was probably carrying less blood than it had originally.

In all these patients the haemoglobin percentage had risen again—in all but one to about its original level (see Table III). In four of the six where we know about the heart size, it had become smaller again, and in three of these the anastomosis was known to have closed. When the haemoglobin rises to its original level and the heart becomes smaller the anastomosis has probably closed. Short descriptions of these patients follow: four of them have obtained good results after subsequent direct operations.

Case A6.—A girl aged 3 lost nearly all her improvement suddenly after pneumonia in the seventh year. The anastomosis was thought to have thrombosed.

Case A15.—A boy aged 10 did well till he had three epileptiform fits in the fifth year: during the next two years he lost ground and the continuous murmur became inaudible. He died after pulmonary valvotomy, with cerebral softening; at necropsy the anastomosis had closed.

TABLE III.—Some Details of Patients who Lost All the Improvement Produced by Anastomotic Operations

Case No.	Anastomosis	Time of Deterioration	Hb Percentage			Heart Size (c.t.r.)			Remarks
			Before Op.	After Op.	Final	Before Op.	After Op.	Final	
A6	Closed	7th year, after pneumonia	157	110	141	49	54	51	2nd op. Good
A15	"	5th and 6th years	142	109	150	48	50	45	" Died
A44	"	7th partly; 9th year all	142	102	130	Erratic			" Good
A143	"	5th year during 5 months	100*	105	130	46	48	—	" "
A147	"	5th year slightly; 6th mainly	143	90	119	41	43	—	" "
A45	Nearly closed	4th to 7th years gradual	117	103	139	54	55	42	" Died
A40	Open	6th year partly; 7th all, after pneumonia	140	104	148	51	54	57	" Good
A47	"	? 5th and 6th years	136	—	—	50	—	—	" "
A54	Open	7th year mainly	100*	101	129	53	56	53	" "
A82	"	5th to 7th years, after nephritis	130	108	120	47	47	57	" Died

* Presumably anaemic.

Case A44.—A girl aged 10 lost some ground in the seventh year. In the ninth year she had to give up her work, having become cyanotic again and having lost all her improvement within a few months: the continuous murmur could no longer be heard.

Case A143.—A girl aged 10 became almost acyanotic and could walk three miles. During the course of five months in the fifth year she lost all her improvement and the anastomosis had closed without any obvious reason.

Case A147.—A girl, aged 16, remained well for five years. After this she became bluer and more short of breath, and some months later had to give up her work: no continuous murmur could be heard.

Case A45.—A boy aged 3 obtained a very good result. In the fourth year his mother thought he was not as well, and by the sixth year there was no doubt about this: the haemoglobin was higher (123%) and the heart was smaller (c.t.r. 48%). His continuous murmur was still as loud, but this was not so in the seventh year, when he had become as disabled and as cyanosed as ever: the heart was even smaller (c.t.r. 42%) and the haemoglobin 139%. A severe high infundibular stenosis was resected, but he died two days later. At necropsy the lumen of the anastomosis admitted a probe only.

Case A40.—A boy aged 8 remained well for six years. Then he could do rather less and his headaches recurred; some months later he had "pneumonia," after which he lost all his improvement and resumed squatting. It seemed likely that the anastomosis had closed, but the heart had not become smaller and the murmur was as loud as before. There must, I think, have been increasingly severe stenosis, though a year later, when admitted for a direct operation, which was very successful, the continuous murmur could no longer be heard.

Case A47.—A Cypriot boy aged 11 did well for five years. In the sixth year he lost most of his improvement, but we do not know if the continuous murmur can still be heard.

Case A54.—A girl aged 5 lost some ground in the fourth year after a cortical thrombophlebitis, but the result was still good. She lost most of her improvement in the seventh year, mainly in one month. Her smaller heart and higher haemoglobin suggested the anastomosis was closing, but the continuous murmur remained quite loud.

Case A82.—A girl aged 5 remained very well for five years, but then lost ground after scarlet fever and nephritis, and more so during the next two years though the continuous murmur was still loud: her heart became steadily larger, and she often complained of swelling of the ankles and had some albuminuria. She died after an infundibular resection. At necropsy there was nothing to suggest occlusion of the anastomosis before its recent ligation. Her deterioration seems to have been due to increasingly severe infundibular stenosis, the passage having become almost atresic.

Loss of Much Improvement

The anastomotic channel had not closed in any of these seven cases, but, certainly in the first and probably in others, it was carrying less blood to the lungs. In the first two the continuous murmur was less easy to hear. In all except the last, the haemoglobin had increased, and in two (Cases A41 and A120) the heart had become smaller; by analogy this made us think the anastomosis was closing, but in both it proved to be open at operation. We think, therefore, that many of them were worse because the stenosis was becoming more severe. Some details are given in Table IV. Only two are described briefly, the first as an example of partial thrombosis of her anastomosis at necropsy, and the second as evidence of increasingly severe stenosis.

Case A46.—A girl aged 16 could walk three miles and worked as a telephonist for six years, though before operation trivial

exertion provoked cyanotic attacks with unconsciousness. During the sixth to ninth years she lost much of her improvement. Her continuous murmur was heard less easily and her haemoglobin had risen again. She died from cardiac arrest a day after infundibular resection. At necropsy the anastomosis was only partly occluded by a firmly adherent thrombus.

Case A120.—A boy aged 3 lost much, but not all, of his improvement in several stages during the seventh and eighth years. Recently he was taken to America for operation by Mr. Kirklin with an extracorporeal circulation. In spite of the small heart and rising haemoglobin percentage, the continuous murmur was well heard and the anastomosis was found to be functioning well. There was a very severe infundibular stenosis, with an orifice that was almost pin-point, and the ventricular septal defect was large and at the usual site. So far, he is doing well.

Second Operations

Ten of the 17 who lost all or much of the improvement have already had direct operations: six obtained very good results, but the other four died. For some time a direct operation after an anastomotic one that had failed proved disappointing, and the mortality is still much higher than for primary direct operations.

Two other patients have had second operations because their original disability had been so extreme that even after great improvement they still needed more. One has improved greatly, but the second has not benefited.

Progress of 21 Patients who Obtained Little or No Benefit

The four patients in whom no operation was possible, five who were not improved, and 12 only somewhat improved, making 21 in all, can to some extent serve as a control. Eight of these 21 have died. Two proved to have a single ventricle and pulmonary stenosis; a third died with meningitis, and a fourth with a pulmonary abscess, all within 18 months of operation. These four were reported in our previous paper, and four have died since. One boy who was very disabled and had frequent fits died three years later. One boy, who after two years had a second anastomotic operation that did not help much, died suddenly five years later. One woman, aged 29, gradually relapsed and died five years later. The eighth was in hospital several times with congestive failure, and died with this six years after: her heart was large for an uncomplicated Fallot's tetralogy, and we think she had some additional lesion.

Four patients lost even the slight improvement they had gained at two to six years after operation. This was due to the anastomosis closing. Four others were much the same for three or four years, when they had second operations; and second operations may be needed in the remaining five, who are much the same after from six to nine years.

In summary, the prognosis of these 21 patients has proved poor. Eight (38%) died after an average period of three years, only three living longer than this. Seven are much the same as before, and six had a subsequent operation, so that the period of follow-up was abridged: two of these had anastomotic operations that did not help much and four had direct operations, of which two proved fatal and two produced good results.

TABLE IV.—Patients who have Lost Much of the Improvement

Case No.	Anastomosis	Time of Deterioration	Hb Percentage			Heart Size (c.t.r.)			Remarks
			Before Op.	After Op.	Final	Before Op.	After Op.	Final	
A46	Less	Gradual 6th to 9th years	135	108	122	47	52	52	2nd op. Died
A153	? Less	Gradual 4th year	120	95	118	48	49	50	
A41	Open	6th and 7th years: severe infundibular stenosis ..	128	114	130	50	51	46	2nd op. Good
A61	"	6th year, after transient hemiplegia	151	116	166	49	51	53	
A108	"	Gradual 6th and 7th years	157	105	120	54	60	57	Recent op.
A120	"	7th and 8th years	150	110	145	51	54	51	
A132	"	8th year, more dyspnoeic and syncopal attacks ..	154	100	90	54	55	55	

It would not be fair to take these as representative of untreated Fallot's tetralogy, because some of them had more complex lesions, and this may have been partly why they did not benefit much from their operations. They do, however, show a striking contrast with the patients who obtained good results.

DIRECT OPERATIONS FOR FALLOT'S TETRALOGY

The results of pulmonary valvotomy and infundibular resection in the first 100 patients operated on by Sir Russell Brock have been reported (Campbell *et al.*, 1954). The operative mortality was 15%; there was little or no improvement in 14%, and a good result in 71%—figures that were not very different from those after anastomotic operations, except that the operative mortality was higher. Our conclusions were based mainly on the 61 patients that had been treated at Guy's Hospital.

We are now reporting a longer follow-up of these 61 patients and adding another 50 operated on in 1953-6, making 111 in all. The operation was mainly infundibular resection in 47, mainly valvotomy in 42, or both procedures in 22 cases. Infundibular resection, which at one time had a higher operative mortality, has now become about the same; but perhaps rather surprisingly it is followed by a good result more regularly; otherwise there was not much difference in these groups, so they have been considered together for most purposes.

Of the 111 patients, 19 died at or soon after operation, 13 obtained little or no improvement, and 79 (71%) obtained good results. None of these 79 has been lost sight of, and they have been followed for an average period of nearly five years—32 for from six to nine years, and all but seven for two years or more.

The operative mortality was higher than for anastomotic operations—17% for all, but 12% for those operated on since 1952. If we exclude 11 who had second operations in which the mortality has been twice as high, it is further reduced to 15 and to 10% respectively. The number with slight or no improvement is 12%—about the same as in the other series. Sometimes this may be because there are other abnormalities that have not been diagnosed or because of some feature that makes surgical correction difficult. Here, too, however, the proportion has been falling in recent years, especially since the fuller realization of the importance of infundibular stenosis even when at first the stenosis appears to be mainly valvular.

Good Results Maintained

Of the 79 who obtained good results, 70 (89%) have remained well during the subsequent years, including most of the earlier patients.

Infundibular Resection

The first eight who had successful results after *infundibular resection* were given in detail in our previous paper, and, partly because I know them so much better than the later ones and know what they can do, their present condition is given briefly (see also Table V).

*Case IR1.**—A girl, aged 13, has kept well for nine years and is now working as a dressmaker, but does not attempt more than this, and leads a quiet home life.

Case IR2.—A young woman, aged 20, is much more active, but her heart is larger (c.t.r. 58%) and she is limited by paroxysmal tachycardia if she does too much.

Case IR3.—A young man aged 19 could do very little, but now is very active and earns his living in Rhodesia. In the ninth year he had bacterial endocarditis, but is able to do just as much after it, though we do not know if his heart, which was still of normal size, has become larger.

*The case numbers are the same as in our previous papers and are the consecutive operations of that particular type. Thus, IR2 indicates the second patient who had infundibular resection without valvotomy. The consecutive V numbers indicate all who had valvotomy with or without infundibular resection as well: they include those with a closed ventricular septum, who are not discussed in this paper.

TABLE V.—Changes in Heart Size and Haemoglobin Percentage in Patients 7 to 9 Years After Direct Operations

Case No.	Heart Size (c.t.r.)			Haemoglobin Percentage		
	Before Op.	After 3-4 Yr.	After 7-9 Yr.	Before Op.	After 3-4 Yr.	After 7-9 Yr.
<i>After Infundibular Resection</i>						
IR1	45	49	49	142	110	105
IR2	56	60	58	120	—	102
IR3	47	47	50	130	112	90
IR6	48	52	—	116	93	—
IR7	48	57	54	133	95	102
IR8	47	53	53	128	111	—
IR10	51	54	53	130	95	90
IR20	45	49	48	115	95	95
IR21	49	63	60	105	84	85
IR22	50	53	55	100*	95	100
Average ..	48.6	53.7	53.2	122	103	101
<i>After Pulmonary Valvotomy</i>						
V2	49	56	58	129	126	126
V3	49	53	53	156	110	104
V10	52	53	50	180	110	111
V20	46	52	53	121	128	142
V25	51	56	53	122	105	103
V32	44	48	53	120	105	103
V34	48	52	51	138	118	103
V35	50	54	50	109	85	97
V42	46	50	47	112	95	94
V48	55	57	55	131	96	100
Average ..	49.0	53.2	52.3	132	110	110
<i>Two Patients Who Have Lost their Improvement</i>						
V22	44	46	46	124	108	117
V29	45	49	48	113	97	116

* Presumably "anaemic."

Case IR4.—A boy aged 14 has kept as well for eight years and is prevented from greater activity more by his mental backwardness than by his heart.

Case IR6.—A boy aged 14 is now working as a shop assistant and cycles and plays tennis.

Case IR7.—A boy aged 12 is now working as a telephone operator and can cycle and play cricket.

Case IR8.—A young woman aged 20 was rather slow in getting her full improvement, but now works in a shop and can walk two miles and go dancing.

Case IR10.—A girl aged 7 is exceptionally good after eight years and leads an active life with no obvious cyanosis.

Case IR21.—A girl aged 15 had an exceptionally good result and lost all her cyanosis, but we feared that the pulmonary flow and the heart were too large. Six years later, however, she is leading a very active life and the heart is smaller (c.t.r. 49 to 66%, but 62% after six years).

The results of recatheterization in Cases IR3, IR7, IR8, and IR21 were included in our earlier paper, and the arterial oxygen saturations had risen to 86, 90, 95, and 98% respectively, and the pulmonary flows to 80, 120, 156, and 208% of the systemic flow. It has been suggested that successful direct operations would convert the condition into Eisenmenger's complex. If the underdeveloped outflow tract became completely unobstructed this would be so, but it still provides enough resistance to prevent this; and the last of these four patients is the only one in whom the pulmonary arterial pressure has risen above normal, and then only to 38/12 mm.

Pulmonary Valvotomy

The early patients who obtained good results after pulmonary valvotomy, with or without infundibular resection as well, are nearly as good.

Case V2.—A girl aged 18 is earning her living as a musician though she still shows obvious cyanosis and has to walk slowly.

Case V3.—A girl aged 11 is more active and leads a normal life without obvious cyanosis after nine years. Looking to the future, however, she has T inversion from V₁ to V₄, suggesting right ventricular strain.

Case V10.—A man aged 22 has kept well and at regular work. Even more significant, his haemoglobin has remained about 111% for eight years, although it was 180% with the consequent risk of cerebral thrombosis.

Case V20.—A boy aged 11 was much improved and later could earn his living and walk four miles, although his haemoglobin did not fall. This, as so often, was a correct guide, for in the sixth year he lost some ground and the haemoglobin rose higher than before (see Table V), but he can still work and walk a mile.

Case V25.—A boy aged 9 does everything at school except the more energetic games which he would like to play, but he developed pulmonary regurgitation after operation and the heart became larger. After seven years the regurgitant murmur is still loud, but he is able to do as much and the heart has become smaller again (c.t.r. 51 to 56 to 53%).

Case V32.—A girl aged 18 has maintained all her improvement: she has married and can carry out her household work.

Case V34.—A boy aged 10 has kept well and is working as a laboratory technician.

Case V35.—A boy aged 14 was improved enough to start as a medical student, and, though delayed by tuberculosis of the lung, he is well and working after seven years.

These patients give a representative picture of the results of direct operations. Case V20 has certainly lost some of this improvement, but, like Cases A55 and A83, not enough to prevent one still calling the result good. With increasing experience the surgeon may succeed in producing good results more regularly, but it seems remarkable how often he did so from the start. I do not think many of the later patients are better than these, and indeed it would be hard to be much better than Cases IR3 or V3 or several others. After recent operations there are, however, fewer of the disappointing results that show some improvement but not enough to be called good.

Good Results Lost

Patients Who Have Died

Only 2 of the 79 patients have died. A woman aged 31 was much improved, but died nine months later with Landrey's acute ascending myelitis (Case IR19). A boy aged 9 could walk two miles instead of 100 yards, but in the fifth year he became ill and was thought to have hydrocephalus. At necropsy the brain was flattened by gross dilatation of the ventricles, and the hydrocephalus was attributed to the attack of basal meningitis two years before his valvotomy (Case V51).

Loss of All or Much Improvement

Only two patients have lost all their improvement, but five have lost much of it. Those who have had direct operations are not, of course, exposed to the risk of the anastomosis closing and there is little evidence of re-stenosis at the site of the operation. We think that some patients who have lost ground in both groups are examples of the natural tendency in Fallot's tetralogy for the stenosis to become more severe as the patient gets older.

Short notes about the patients who have lost their improvement follow. The first of these patients, one of the only two who had lost it all, is reported on more fully because the infundibular stenosis must have increased after operation in spite of the larger flow through her pulmonary valve. The sixth girl was beginning to show the effects of her large left-to-right shunt in the same way as Case A25, who died in the tenth year after an anastomotic operation. The seventh and last patient who lost ground (Case V91) seems to have done so because of pulmonary regurgitation.

Case V29.—A girl aged 17 could do a full day's work and go dancing after it: her haemoglobin fell and her heart became larger (see Table V). After "influenza" in the third year she could manage only half-time work. Catheterization showed that the gradient was mainly between the right ventricle (110/0) and the infundibulum (30/0) and only slightly between this and the pulmonary trunk (12/3)—figures much the same as those found at her second operation three years later. She still kept some of her improvement, but in the fourth year she had to give up work and was as bad as ever. Clearly the failure to relieve her infundibular stenosis meant that the operation had been incomplete, but the great improvement for three years and its subsequent loss show that this must have become worse and it was found to be very severe when subsequently she had a successful infundibular resection.

Case V22.—A girl aged 12 had an excellent result and could lead a normal life, sometimes walking as far as nine miles. After "influenza" in the fifth year she could walk no more than a mile. In the sixth year she became worse again and was little, if any, better than at the start.

Case IR25.—A boy aged 9 could walk a mile and attend school regularly. In the fifth year he could not get about so well, and his haemoglobin had risen from 104 to 119%.

Case IR41.—A boy aged 2 was so disabled with frequent attacks of unconsciousness that pulmonary atresia seemed likely. He became much better, both in colour and in capacity, and this lasted for two years. After this he could not walk more than 50 yards and squatted more often, though the attacks of unconsciousness did not recur.

Case V113.—A boy aged 5 was much improved, though he still squatted sometimes. After five years he could not do so much and his heart was smaller (c.t.r. 52 instead of 57%), but this may have been due to the growth of his chest. This patient and the next one had infundibular resection as well.

Case V117.—A girl aged 9 could walk only 50 yards. After open cardiectomy she was greatly improved and lost all her cyanosis, but the heart enlarged more than usual (c.t.r. 48 to 60%). Four years later she still seemed well, but her lungs were pleonæmic with a hilar dance and the heart was still as large. She was more dyspnoeic, and sometimes after doing too much was orthopnoeic at night.

Pulmonary Regurgitation

This has proved a less important complication than was feared—much less important with pulmonary than with aortic valvotomy, presumably because the relevant pressures are so much lower and the valve is rarely calcified. Pulmonary regurgitation of significant degree has occurred in three patients. In the first (Case V25) and in the second it did not seem very important, but in the third it was.

Case V60.—A boy aged 7 has maintained his good result for six years, but his heart has stayed larger (c.t.r. 48 to 57%).

Case V91.—A girl aged 12 was greatly improved after operation, but developed pulmonary regurgitation. A year later, after pleurisy, she became increasingly dyspnoeic. After another year she was readmitted with a loud pulmonary diastolic murmur, a raised venous pressure, and a greatly enlarged liver; her heart had become enormous (c.t.r. 51 to 71%). With rest, salt restriction, digitalis, and mersalyl she improved, but it seemed that she would be permanently disabled. She gradually improved, however, and a year later was able to stop all treatment except digitalis and to resume work as a dressmaker, though her liver was still palpable: her heart has become smaller again (c.t.r. 64%). In retrospect it seems that she might have had some infection with a pericardial effusion, but there was no other evidence of this.

OBJECTIVE EFFECTS OF BOTH OPERATIONS

The success of these operations has been judged subjectively by the improvement in the patient's capacity and colour. This is the best way when the doctor knows his patients well, for it measures the essential change. In our earlier follow-up there was good correlation between this subjective judgment and the objective changes in the polycythaemia and haemoglobin percentage. The more important findings—the continuous murmur, squatting, the haemoglobin percentage, and the size of the heart—are now discussed. All these, except the first, apply equally to anastomotic and to direct operations.

Physical Signs.—An easily heard continuous murmur indicates a good flow through the anastomosis. If it becomes more difficult to hear, the flow to the lungs is smaller and it is likely to become inaudible: then there are generally other reasons for thinking that the anastomosis has closed. A large flow will often produce some increase in the pulse pressure, but a patient may obtain a very good result without this, and an easily heard continuous murmur is generally a more useful sign. The auscultatory signs are not much use in judging the results of direct operations, and it is still possible to diagnose some stenosis in most of the successful cases; further, a loud murmur may be due to the irregularity of the outflow tract after operation rather than to the severity of the obstruction.

Squatting.—When the result is good the patient ceases to squat: it is surprising that a habit so long-established should be stopped so suddenly. Patients forget about it and may seem surprised when they are questioned on it. Older patients may, however, force themselves to stop squatting for social reasons, so its absence is not always reliable. Resumption of the habit always means that the patient has become worse and often that he has lost all his improvement.

Haemoglobin Percentage and Polycythaemia.—A fall towards normal in the haemoglobin percentage and in the red-cell count is generally a reliable sign of a better blood flow to the lungs and of less anoxaemia. They will, of course, fall if the patient becomes anaemic from loss of blood or otherwise, and then he is worse off. Sometimes the real degree of anoxaemia is more severe than is suggested by the relatively small increase of haemoglobin, because the patient is "anaemic": a red-cell count that is high in relation to the haemoglobin percentage will often give an indication of this. Otherwise, any subsequent rise is a reason for thinking the patient is not as well as before.

In our earlier series the mean haemoglobin of all the patients with good results fell from just under 130 to 103%, and the fall was almost the same for anastomotic as for direct operations. The percentage was generally between 120 and 159 before operation and between 90 and 119 after it, though there was, of course, a wide range.

Most of the patients with good results have maintained this improvement in their colour and in their blood count. In some, however, who have not lost their improved capacity the haemoglobin has risen above the lowest level to which it had fallen. There is more evidence of this after anastomotic than after direct operations. In 50 cases of the former the average haemoglobin fell from 132 to 104% after three to four years, and had risen to 111% after eight to ten years. In 20 cases after direct operations it fell from 127 to 107% after three to four years, and was still 106% after seven to nine years, but the difference is small. It could be explained by the anastomosis becoming somewhat smaller or even by its failing to grow as much as the patient.

A rise of haemoglobin to near the original level is one of the most reliable signs that the patient is not doing well, and often means that the anastomosis has closed (see Table III).

The electrocardiogram is not very useful in judging the result. The right ventricular preponderance is not likely to diminish, for the right ventricle is still working against the same high pressure, and the patient's increased activity must increase the work of the right side, and, sometimes perhaps after anastomotic operations, of the left side of the heart as well. There is some tendency, as the years pass, for the T inversion and the signs of right ventricular strain to increase, but the patients with these signs are not showing any harmful effects from them so far. If patients escape the other hazards of Fallot's tetralogy, right-sided failure seems likely to follow some time in the near future, but over the ten-year period this has not been important.

Changes in the Size of the Heart

The increase in the size of the heart after anastomotic operations was noticed almost at once, and at first there was some

fear that this might be progressive and lead to heart failure. The same increase occurs after direct operations. We found that the average change in the cardiothoracic ratio was from 50 to 53% after anastomotic operations and from 48 to 52% after direct operations, with the same wide range of variation after both, and that the increase had generally reached its maximum a month or two after operation and was not progressive (Campbell and Deuchar, 1953; Campbell *et al.*, 1954).

Our observations on the size of the heart in this longer follow-up are not so complete, but include nearly all those who have been followed for from 8 to 10 years. Many of the figures given in Tables II and V show that up to 10 years the increase is rarely progressive and the average size after 8 to 10 years is much the same as after three to four years. Where figures are available the average increase in the cardiothoracic ratio is rather less than one-tenth (from 49 to 53.5% after three to four years and to 53% after 8 to 10 years), and this is the same after anastomotic and after direct operations. These average figures hide large individual variation, as is shown in the Tables, and even in patients with very good results the increase may be less than this or much more.

In Fallot's tetralogy the heart is often small and undeveloped, partly, perhaps, from lack of use. Some increase in its size must be expected if the patient is to have an

FIG. 2.—More usual heart size in two patients nine years after successful operations for Fallot's tetralogy. Both had equally good results clinically, but the increase in the blood flow to the lungs is more obvious in one than in the other, where the lungs are still oligæmic. (A) C.t.r. 51% (12/23.5 cm.) Case A24. (B) C.t.r. 51% (13.5/26.5 cm.) Case A23.

FIG. 3.—Telerradiograms of two patients eight years after anastomotic operations for Fallot's tetralogy. Generally the two lungs seem equally filled, but from the better filling of one lung it is easy to see that the operation was on the left side in one (Case A133) and on the right side in the other (Case A34). The left pulmonary artery was unusually large in A before operation. Both results are extremely good, and the hearts are not unduly enlarged (c.t.r. 54%).

adequate pulmonary blood flow and is to lead a more active life. An increase of one-tenth in the cardiothoracic ratio where it was 45% before operation leaves it of normal size and has no drawbacks, and where it was 50% the same increase leaves it still only slightly enlarged. Examples of both these degrees are given in Figs. 2 and 3. We have no anxiety about an increase to 55 or even 57% unless, as is unusual, it is progressive. With figures over 60% we are more anxious, and such a size is, of course, reached more easily if the heart was large before operation. Patient A25, who was notable from the start as showing pleonaemic lungs and one of the largest hearts (see Fig. 1), illustrates the risk, for she died in the tenth year with congestive heart failure, and we are anxious about the outlook for Case V117. Sometimes, however, the heart may become rather smaller as it becomes habituated to the new conditions, both after anastomotic and after direct operations (see Cases A5 and IR21).

DISCUSSION

Many authors have published their results after operation, but there are few long follow-up studies. The recent one of Taussig and Blalock's cases by White *et al.* (1956) is most valuable, but only 73% of the 500 cases had been traced. Of the 212 patients with Fallot's tetralogy who obtained a good result, 69% have kept this for from five to eight years, 20% have lost ground, and 11% have died during this period, but this is reduced to 9% if second operations are excluded. The great value of successful operation is shown by the contrast of this mortality with one of 44% among those who obtained only fair results from operation. In our series there is a similar contrast with rates of 6 and 38% respectively.

The best age for operation seemed to be between 8 and 12 years, for here the number who had maintained good results reached over 80%. The effect of age, however, is not great in our series, for the figure was 80% in each five-year period except in infants and in those over 20, where the results were less good originally and less well maintained afterwards.

Bacterial endocarditis had occurred in 6% of their series, about 1% per annum, but only 1 in 15 of these patients died. This incidence is higher than in our series, but for cerebral abscess it is much lower than ours. Few of the 33 deaths were due to heart failure; seven were after a second operation and the remainder from a variety of causes.

Potts's Aorto-pulmonary Anastomoses.—The immediate results are not very different from other anastomotic operations—an operative mortality of 9% and a good result in 68%. Only three of my patients have had this variety. Potts *et al.* (1955) have followed up their first 100 cases for about the same period as we have, and find that good results have been maintained at least as well as after other anastomotic operations: there were five deaths—one from a heart attack, one from a brain abscess, one from rheumatic fever, and two from "pneumonia" which may have been partly pulmonary congestion from too large a flow. Though it is not easy to compare the exact degree of enlargement of the heart, it seemed generally to be rather greater, but again was not often progressive.

Comparison of Anastomotic and Direct Operations

No other follow-up study of a large series of patients after direct operations has been found, and in any case it seems better to compare our own patients, who have so far as possible been assessed in the same way. Scientifically, it would have been better if direct operations had been started at the same time and done alternately, but this was not possible. All these anastomotic operations were done in 1947–51. Most of the direct operations were done in 1949–52, but some up to 1956. The selection depended mainly on Sir Russell Brock's view of what was the best surgical procedure at the time, but the earlier patients were, I think, generally the more severe.

The results of direct and anastomotic operations were very similar in our earlier reports, except that the former had a higher operative mortality. This longer follow-up makes them more equal, for there are fewer deaths and fewer complete relapses after direct operations. We thought from an early stage that they more often relieved all the cyanosis, and this is also the view of Wood (1956), but the average reduction in the polycythaemia and haemoglobin level was the same at first and is only a little better maintained after direct operations. The degree of improvement is, however, more varied, from slight or moderate improvement to good or very good results according to the degree of success of the pulmonary valvotomy or infundibular resection. Successful anastomotic operations, on the other hand, tend to produce a more uniform degree of improvement, since the extrapulmonary blood flow through the subclavian anastomosis will generally be proportional to the body size.

The patients who obtained good results but later died or lost ground after each type of operation have been described. Good results have been maintained in 80% after anastomotic and in 89% after direct operations, and this means that the patients were able to work or attend an ordinary school. Allowing for the different length of the follow-ups, the figures for direct operations are not much better, but the real advantage is greater, for the annual death rate and the proportion losing all improvement are only half those after anastomotic operations, the totals being made nearer equality by the larger number who lost only some improvement (see Table VI). It is,

TABLE VI.—Results of Anastomotic and Direct Operations Compared

Operation	Total No. With Good Results Traced	Subsequent Progress				Annual Loss (Percentage)			
		Good Results Maintained	Died	Lost All Improvement	Lost Much Improvement	Died	Lost All Impr.	Lost Much Impr.	Total
Anastomotic	126	101	8	10	7	0.9	1.1	0.7	2.7
Direct	79	70	2	2	5	0.5	0.5	1.4	2.4

however, a more severe test for the latter, because there have been several relapses and deaths during the tenth year, a period that has not yet been reached by many who had direct operations.

The loss of all improvement after anastomotic operations generally occurred because the anastomosis had closed. Sometimes, however, and more often when only some improvement was lost, it seemed due to the natural tendency for the stenosis to become more severe; and this is probably the main reason for the deaths in childhood of those who have not had operations.

None of the deaths was due to the anastomosis closing, except indirectly, when it led to their needing second operations. About one-third were due to heart failure in some form, and probably this was at least hastened by the increased activity of the patients; about one-third were due to incidental causes; and the remaining third to cerebral causes, mainly cerebral abscess.

Cerebral abscess is a well-known complication of Fallot's tetralogy, and we have discussed the reasons (Campbell, 1957). Even so, among 130 patients, three dying from cerebral abscess* and three others making good recoveries after operations for it is a high proportion. We do not think it has any connexion with the anastomosis, except in the broad sense that the patients could lead more active lives with the consequent exposure to fatigue and infection. It is all the more remarkable since during the same period of follow-up only four of these patients suffered from

*Since this was written, two more patients, a boy aged 15 and a girl aged 4, both of whom did well for seven years after anastomotic operations, have died with cerebral abscesses and both in the eighth year after operation. Of the 10 patients who have died, five died with cerebral abscesses.

bacterial endocarditis: all recovered and were no worse afterwards.

So far, no patient who had a successful direct operation has died with a cerebral abscess. A girl aged 3 who was only improved died with convulsions in the second year after pulmonary valvotomy; at necropsy the posterior cusp of a valve that was bicuspid had been split, and a large area of the brain supplied by the middle cerebral artery was necrotic (Case V96). This supports the view that a cerebral abscess may develop from a primary thrombosis (Campbell, 1957), but in this case the thrombosis was so extensive that it led to her death before this could happen.

Future Outlook

Even after a successful operation there is still Fallot's tetralogy, though in a slight rather than a severe form. A larger proportion will reach the stage that one sees occasionally without operation, subjects who can lead a quiet life up to 40 or 50 years. Bedford (1956) reported two such patients whom he had observed for 27 years. One, who died when she was 52, had got on tolerably well until the last four years of her life, when she developed slight congestive failure and cerebral symptoms with increasing cyanosis and dyspnoea. The other was still without failure when she was 52: her haemoglobin had been up to 170% and her cerebral symptoms were relieved from time to time by venesection. White and Sprague (1929) described the well-known example of longevity—the composer Henry Gilbert, who died when he was nearly 60. Marquis (1956), in an important paper on the longevity and the early history of the tetralogy of Fallot, described the case of a woman who lived to the age of 64.

Our oldest patient is now 53: though cyanosed from birth and squatting frequently as a child, she could lead a quiet life at home but could not go to work. Since the age of 48 she has been more breathless and can walk only 100 yards, and, though she has had a large heart (c.t.r. 63%) and gross right ventricular strain with T inversion from V1 to V4 and congestive failure, is losing ground only slowly.

It is possible now to estimate how many of the patients who have had a successful operation are likely to be reasonably active till middle age. Assuming that the number losing ground will continue at the same rate and that the mortality among those who have lost their improvement will be much higher (38% in seven years), a rough forecast of the position after 7, 14, and 21 years, based on our figures for anastomotic operations, is given in Table VII.

TABLE VII.—*Estimated Condition of 100 Patients Who Have Had a Successful Operation for Fallot's Tetralogy*

	Patients Who Will Have Died	Patients Severely or Moderately Disabled	Patients Leading a Satisfactory Quiet Life
After 7 years	6	14	80
„ 14	17 (6+6+5)	19 (14-6+11)	64 (80-16)
„ 21	29 (17+8+4)	20 (19-8+9)	51 (64-13)
31.5 years (average age)			

We think that half the patients who obtained good results will be reasonably well after 21 years, but the average age will still be only about 31 years. Perhaps one-quarter will be able to carry on in this way till they are 50; but this is even more speculative, and is mentioned only in the hope that someone will prove or disprove it by following the patients for another twenty years. The proportion maintaining their good results after direct operations should become relatively higher as the years pass, for, so far, fewer have died or lost all their improvement. The number of these patients who are able to work and enjoy life in a way that was impossible before is even more important than the prolongation of life.

SUMMARY AND CONCLUSIONS

Some of the patients who obtained a good result after an anastomotic or after a direct operation for Fallot's tetralogy have lost all or part of their improvement during the subsequent 8 to 10 years. Often this is due to the inevitable risks of the condition, for all these patients still have Fallot's tetralogy, though the stenosis has to some extent been relieved, directly or indirectly. These causes, especially cerebral complications, were responsible for more than a third of the deaths; the heart could not support the increased pulmonary flow and the increased activity that it allowed in another third; but in the final third the cause was not directly related to the heart condition or to the operation. In many patients who lost all their improvement after anastomotic operations, however, this was due to the anastomosis closing. In others, and in most of those who lost some of their improvement after both sorts of operations, it seemed to be due to the tendency for the stenosis to become more severe.

Of those who obtained good results, 80% have maintained them for an average period of seven years after anastomotic operations and 89% for five years after direct operations. The long-term advantage of the latter is greater than appears from these figures, for there were only half as many deaths and half as many who lost all their improvement with direct as with anastomotic operations. We think that perhaps half of those who obtained good results may be reasonably well 20 years after operation.

After anastomotic operations, increasing difficulty in hearing the continuous murmur is a bad sign, and if it cannot be heard the anastomosis has probably closed. The auscultatory signs after direct operations are not so much help.

The reduction in the anoxaemia and resultant polycythaemia and high haemoglobin percentage that was found three or four years after operation has been maintained in most patients for the six to ten years of this longer follow-up, but not, of course, in those who had lost their clinical improvement.

The heart increases in size within a few weeks after a successful anastomotic or direct operation. On the average the cardiothoracic ratio increases by one-tenth (49 to 54%) and remains at this level for 8 to 10 years. There are no drawbacks to some increase in the size of the smaller hearts. The ideal is a limited increase, large enough to indicate a reasonable pulmonary flow that will enable the patient to do more, but not large enough to throw an undue strain on the heart, and this is generally about 10%: it is unlikely to be progressive and there is no reason to be anxious about it. In fact, if a heart that has become larger returns to near its original size, especially if the haemoglobin returns to its original level, the anastomosis has probably closed or the increased pulmonary flow has been lost by the stenosis becoming more severe.

Neither of these operations for Fallot's tetralogy is curative, for, of course, the ventricular septal defect remains and the right ventricle is working against the systemic pressure. These results show, however, that generally they produce great improvement that lasts for many years. The good results after direct operations suggest that when the ventricular septal defect can be closed it should not be difficult to relieve the infundibular or valvular stenosis.

It is a pleasure to thank Sir Russell Brock, not only for his outstanding work in developing these direct operations, but for allowing and even encouraging me to judge the success of his results; also Dr. Charles Baker for his help and for the inclusion of some of his patients; and Mr. Holmes Sellors and Mr. Ian Hill for operating on some and for keeping me so well informed about what they had done. I also thank Drs. S. S. Suzman, Geoffrey Reynolds, and D. C. Deuchar for help at different stages in the follow-up of so many patients for up to ten years, and Drs. Deuchar, R. J. Shephard, and L. Brotmacher and the registrars at the National Heart Hospital for the results of catheterization.

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VACCINATION AGAINST POLIO-MYELITIS WITH LIVE VIRUS VACCINES

4. A REVIEW OF THE PRESENT POSITION

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In a report recently published by the World Health Organization (1958), the Expert Committee on Poliomyelitis strongly recommended that controlled field trials of live attenuated poliovirus vaccines should be carried out. The committee suggested suitable circumstances and populations for the trials and specified the strains of virus which it considered should be used. Trials are now in progress in many parts of the world, and a preliminary report of one of them has already been published (Courtois, Flack, Jervis, Koprowski, and Ninane, 1958). The purpose of this review is to give the reader who is unfamiliar with the subject some idea of the progress that has been made in the development and testing of attenuated poliomyelitis vaccines.

The possible advantages of living attenuated poliovirus vaccines over formalinized vaccines (Salk type) are that they can be given by mouth, that they are cheaper to produce, and that they may give a better immunity. They certainly give a broader type of immunity which will for a time prevent or modify subsequent infection of the alimentary tract with poliovirus. This is in contrast to the immunity at present produced by vaccination with formalinized vaccines which does not modify subsequent alimentary infection, at any rate to the same degree. The difference in the immunity produced by the currently available formalinized vaccines and attenuated virus vaccines is important because the use of attenuated virus vaccines in a community might interfere with the natural spread of virus, and so far there is no evidence that formalinized vaccine is capable of doing this (Langmuir, 1957; Fox, 1957a, 1957b).

In the last few years there have been a number of small laboratory-studied trials of attenuated poliovirus

vaccines, and there has been much progress in their development (Sabin, 1957a, 1957b), but the rapid emergence of a successful formalinized vaccine in 1955 removed some of the urgency which might have led to their earlier trial in the field. This delay allowed time for cautious progress, which may have been a good thing because attenuated poliovirus vaccines have certain novel features not previously encountered in human vaccines.

The poliovirus strains incorporated in current living vaccines developed by Sabin (1957b), by Cox and his associates (see da Silva, McKelvey, Bauer, Prem, Cooney, and Johnson, 1957), and by Koprowski (1957) have all been grown in monkey-kidney-tissue culture and selected for their comparative lack of neurotropism when inoculated into the C.N.S. of monkeys in large amounts. The vaccine viruses are given orally and cause an inapparent infection. They multiply in the alimentary tract like natural polioviruses, and the vaccinated subjects develop an immunity which is probably similar to that following an infection with one of the less invasive naturally occurring strains.

Attenuated poliovirus vaccines, like any other vaccines, require testing in the field for safety and effectiveness, both to the individuals vaccinated and to the community as a whole. For reasons of clarity these different aspects are considered separately.

Safety to the Vaccinee

The safety of attenuated poliovirus vaccines to vaccinees has been assessed both by direct clinical observation and, indirectly, by studying alterations which may occur in the character of the vaccine virus after multiplication in the human host.

To the best of our knowledge no illness definitely attributable to the use of attenuated poliovirus vaccines has so far been reported among thousands of persons who were observed carefully after vaccination in different trials with several different attenuated virus vaccines. This is a most encouraging fact, but we must bear in mind that nearly all natural poliomyelitis infections are mild or inapparent, especially with types II and III poliovirus, and that many of the people vaccinated in these trials have either been immune before vaccination or have been selected in a manner which has been far from ideal.

The indirect assessment of safety is made by testing the properties of the virus excreted by vaccinees. While there is a wide spectrum of monkey neuropathogenicity among naturally occurring or wild polioviruses, markedly neurotropic strains have always been recovered from the faeces of paralysed patients. If the excreted vaccine virus remains considerably less neurotropic for monkeys than wild polioviruses, which have been isolated from the faeces of paralytic cases, then it is usual to presume that the vaccine virus will do no harm to the vaccinee.

So far only one vaccine virus has been shown to change greatly in its neurotropism after growth in the human gut (Dane, Dick, Connolly, Fisher, and McKeown, 1957). This was the rodent-adapted TN type II poliovirus (Koprowski, Norton, Jervis, Nelson, Chadwick, Nelsen, and Meyer, 1956), and there is general agreement that it is unsuitable for further trial (Dick and Dane, 1957; World Health Organization, 1958). All the other vaccine viruses which have been grown in monkey-kidney tissue culture and have been tested have shown some change towards greater neurotropism, but these changes have been insufficient to cause anxiety for the safety of vaccinees. If safety for the individuals receiving vaccine were all that was required of a vaccine, then there would be few problems in planning progressively larger trials of the currently available attenuated strains, though opinions would vary on the relative importance of direct clinical assessment and the indirect laboratory