The heart tends to become larger after direct as after anastomotic operations, the cardiothoracic ratio rising from a mean of about 49 to 53.5% within a few months of operation and remaining at or a little below this level during the next few years. When the clinical result is particularly good and the cyanosis is abolished, the heart may increase in size more than usual, as after an unusually large anastomosis. It would be optimistic to expect the improvement that follows either of these operations without some increase in the size of the heart, because the right ventricle is still working against the systemic pressure and the patient is leading a much more active life. It means that in the patients with the best results the doctor should act as a restraining influence, persuading them to lead a reasonably quiet life if they wish to keep their improvement as long as possible.

It has been suggested as a criticism that direct relief of the stenosis will raise the pulmonary pressure and produce a condition like Eisenmenger's complex. This is not so. Even when the blood flow to the lungs is greatly increased and the patient can do much more, the stenosis has not been relieved so completely that the high pressure of the right ventricle is transmitted to the pulmonary trunk. In most cases, although the larger pulmonary flow and the condition of the pulmonary artery felt at operation and seen on radioscopy all show that the obstruction is less, catheterization shows that there is still a large pressure gradient across the site of the stenosis. In one patient only—one who can do all she wants and is acyanotic, with her right-to-left shunt reversed—there is some rise of pressure in the pulmonary trunk, but the increase is not very great.

The striking improvement as the result of increasing, directly or indirectly, the blood flow to the lungs has perhaps overemphasized the stenosis and drawn attention away from the ventricular septal defect and the overriding aorta. The improvement in the cyanosis shows that the venous shunt to the aorta is much less, and this has been confirmed by catheterization in several cases, though, of course, the pressure in the right ventricle remains about the same. But, so long as the ventricular septal defect remains, the right ventricle will have increased work and will be exposed to the risk of strain.

Future difficulties, however, are no reason for withholding the great advantages that anastomotic and direct operation can give, though clearly the treatment of Fallot's tetralogy will not be ideal until the ventricular septal defect can be closed.

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SOME NEUROPHYSIOLOGICAL ASPECTS OF SEROTONIN

BY

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During the past few years a number of investigations have revealed that serotonin is of importance in the functioning of the autonomic and central nervous systems, and that the neurogenic behaviour of animals can be profoundly influenced by pharmacological agents which interfere with the action of this compound. The purpose of this paper is to summarize several of these findings.

The existence of serotonin was discovered only a few years ago as a result of two quite independent lines of work. Rapport, Green, and Page (1948) attempted the isolation of the vasoconstrictor which has long been known to form in mammalian serum when blood clots. They succeeded in crystallizing the substance present in serum which exerted this effect on the vascular bed and named it "serotonin." Rapport (1949) continued the study of the chemical nature of the active substance, and was able to deduce that it was 5-hydroxytryptamine (see Fig. 1). The correctness of this formulation was confirmed by Hamlin and Fischer (1951) and by Speeter *et al.* (1951), who synthesized 5-hydroxytryptamine and showed that it was identical with the naturally occurring substance.

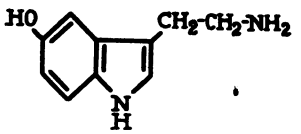

FIG. 1.—Structure of serotonin.

While the work on the identification of the vasoconstrictor of serum was being done, Erspamer (1940), in Italy, had been investigating a constituent of animal tissues which he had named "enteramine." This material occurred in gastric and enteric mucosa of mammals, and in the skin and salivary glands of such lower forms as toads, salamanders, and octopi (Erspamer, 1952; Erspamer and Vialli, 1952). The distinctive staining properties of the argentaffin cells of gastric mucosa were attributed to this substance, and these staining properties were used to follow it in early attempts at isolation. Pharmacological properties of crude extracts containing enteramine were found in that such extracts caused various smooth muscles to contract. Such properties led Erspamer to the view that the active agent was a hormone. Using pharmacological tests and colour reactions as guides, Erspamer and Asero (1952) were able to isolate a pure compound from the salivary glands of the octopus. This compound was found to be 5-hydroxytryptamine, identical with serotonin.

Action on Smooth Muscle

The early work on serotonin, or enteramine, had clearly indicated that it caused smooth muscles to contract. As soon as abundant material became available through chemical synthesis a variety of pharmacological effects of it began to be reported. Thus, segments of carotid arteries of sheep (Reid and Rand, 1952; Woolley

and Shaw, 1952, 1953a) or intestinal strips or isolated uteri of rats or of guinea-pigs (Erspamer, 1952) were made to contract when exposed to serotonin in minute concentrations (0.2–0.02 μg. per ml.). The history of serotonin as a vasoconstrictor has prompted a large number of studies with it in whole animals. One would expect it to cause a rise in blood pressure as a result of a decrease in the internal diameter of the blood vessels, and, in fact, in some species it does act as a pressor agent. Thus in dogs (Page, 1952; Freyburger *et al.*, 1952; Woolley and Shaw, 1953b) or in man (Page and McCubbin, 1953) the intravenous injection of serotonin leads to a sharp rise in blood pressure. The effect in dogs, however, is biphasic. Usually, but not invariably, the arterial pressure falls for a period of 10–20 seconds following the intravenous installation, and then the rise ensues. With small doses (e.g., with 10 μg. per kg.) one may see only the fall. In cats the fall in pressure is more prominent than the rise (Page, 1952; Freyburger *et al.*, 1952; Reid, 1952).

Several explanations have been advanced for the biphasic nature of the changes in blood pressure elicited by serotonin, but the one which seems best suited to the findings, and which will serve to introduce us to serotonin in neurophysiology, is derived from the work of Page (1952). He found that the fall in pressure was abolished by vagotomy, or by pharmacological blockade of the autonomic nerves with drugs such as tetraethylammonium chloride or atropine. In animals so treated, intravenous serotonin called forth only a rise in blood pressure. Furthermore, such animals were affected by considerably smaller amounts of serotonin (Page and McCubbin, 1953).

It would seem that the injection of serotonin into the blood stream sets up a reflex stimulation which then appears as a compensatory vasodilatation possibly directed towards the maintenance of normal pressure. When this stimulation is large or progressively increasing as in the intravenous injection experiments, the reflex vasodilatation overcompensates and one sees the transient fall in pressure. However, this compensatory mechanism has a limit and if the quantities of serotonin are large enough to evoke much contraction of the smooth muscles of the vascular bed it is obliterated and one sees the rise in pressure as a result of these contractions.

Direct evidence for the initiation of a nerve impulse was obtained by Schneider and Yonkman (1953). They succeeded in recording prolonged electrical discharges in the vagus of cats injected intravenously with serotonin. The locations of the receptors which initiate such nerve impulses are not entirely settled, but it is clear from the work of Page (1952) that they are not uniformly distributed in the body. Present evidence (Comroe *et al.*, 1953; Dawes, 1953; Ginzel and Kottegoda, 1954) suggests that there are such receptors in the carotid sinus, the lungs, and the heart. Possibly the excitation arises from the initiation of contraction of the muscles in the vessel walls as serotonin reaches them, but more probably the hormone actuates these special receptors in distinctive positions in the circulatory system.

Functions in the Nervous System

We emerge now from a brief consideration of the effects of serotonin on smooth muscles to an examination of it in the nervous system. The evidence collected thus far is of three kinds: (*a*) serotonin occurs in the brain, and in stellate and other visceral ganglia. In some of these sites it occurs in surprisingly high concentration. (*b*) Stimulation of certain peripheral nerves leads to the release from the brain, and in other experiments from ganglia, of a substance which appears to be serotonin. This substance then acts on target organs such as the heart. (*c*) Some specifically acting drugs have been discovered which antagonize the action of serotonin on smooth muscles. These drugs cause mental aberrations in man and in laboratory animals.

The occurrence of serotonin in the nervous system is now well established. From the brains of dogs, Twarog and Page (1953) were able to obtain a substance which exhibited the pharmacological effects of serotonin. This material was extracted with organic solvents and separated from impurities by chromatography on paper. The isolated substance showed the pharmacological properties of serotonin, had the correct R_f, and gave the anticipated colour reactions. Amin, Crawford, and Gaddum (1953) also were able to adduce evidence for and to measure serotonin in various parts of the brain. In the stellate ganglia of several invertebrates Florey and Florey (1953, 1954) found a surprisingly large amount of serotonin, which was isolated by paper chromatography and identified. Similarly, Welsh (1954) was able to demonstrate serotonin in the visceral ganglia of the shellfish *Venus mercenaria*.

The functioning of serotonin in the nervous system is just now being discovered. Consequently, knowledge is fragmentary, but seems to portend a large number of subsequent investigations. It has been known for many years that the stimulation of the cut end of the vagus nerve may lead to the release of a pressor substance into the venous blood from the head. Taylor, Page, and Corcoran (1951) thought that this might be serotonin. Their experiment was as follows. Both vagi of a dog were cut and the spinal cord was destroyed below C 6. The venous return from the head of this dog was then conducted into a second dog through a connexion for cross-circulation. This second animal was to act as indicator. When the cut end of the vagus of the first dog was stimulated electrically the arterial pressure of the second, or indicator, dog rose. The stimulation of the vagus of the first dog had thus caused something to be released from its brain into the circulation, and this raised the pressure in the second dog. Taylor *et al.* felt that this substance might be serotonin, and for the following reason. The rise in pressure of the second dog was eliminated by the introduction of 1-hydrazinophthalazine. Prior experiments had shown that this same drug would prevent the rise in arterial pressure which is elicited by serotonin. The possibility that the pressor substance was adrenaline, *nor*-adrenaline, or angiotonin was excluded by use of appropriate drugs. There was no direct proof that it was serotonin.

An experiment of Welsh (1954) in the shellfish *Venus mercenaria* provided further evidence of a functional role for serotonin in the nervous system. The heart of *V. mercenaria* is accelerated by minute amounts of serotonin. This is best seen when an anti-acetylcholine is simultaneously employed to eliminate the retarding effect of this latter hormone on the heart rate. If now the visceral ganglion is stimulated electrically the heart rate is accelerated, just as it is by administration of serotonin. The acceleration could, of course, be due to many things, but a further experiment suggested that it was due to serotonin. The action of the excitor substance liberated from the ganglion by electrical stimulation was prevented by ergotamine. This drug was known from the prior work of Shaw and Woolley (1953) and of Fingl and Gaddum (1953) to be a specific antagonist of serotonin. Thus it would seem that electrical stimulation of the visceral ganglion leads to the release of serotonin, which shows itself by stimulation of the heart rate. The abundant occurrence of serotonin in the ganglia which was demonstrated would be consonant with such a view. The possibility that adrenaline was the active participant was eliminated by the demonstration that adrenaline did not affect the heart rate under the conditions used (cf. Twarog and Page, 1953).

Antimetabolites of Serotonin

The functional participation of serotonin in the brain, especially in certain mental processes, has been suggested as a result of pharmacological evidence (Woolley and Shaw, 1954). It is now being widely recognized (cf. Woolley, 1952) that some drugs owe their effects on living things to the fact that they are related in chemical structure to one or another of the hormones, vitamins, or other essential cell constituents, and that, by virtue of this relationship, they are able to block the specific action of the cell constituent. They thus produce a specific deficiency of the hormone to which they are related. Such drugs are called antimetabolites. Some of them have been formed synthetically by changing slightly the chemical structure of a given hormone or vitamin. Others have been recognized to occur in nature among the host of drugs of plant and animal origin. In these latter the structural analogy to the target hormone or vitamin is generally less clear than among the synthetic antimetabolites. The natural products are usually more complex derivatives.

Both synthetic and naturally occurring antimetabolites of serotonin have been found. Immediately after the final proof of structure of serotonin was announced, a programme for the elaboration of antimetabolites of it was begun in the belief that such agents would almost surely be useful in the fundamental studies of the action of this hormone, as well as practically in the pharmacological manipulation of its functioning. Several near relatives of serotonin, such as the one shown in Fig. 2 (Shaw and Woolley, 1954), were synthesized, and were demonstrated to antagonize the action of the hormone on various smooth muscles examined *in vitro* (Woolley and Shaw, 1952, 1953a). Some of these compounds were found to prevent the rise in blood pressure caused by serotonin in dogs (Woolley and Shaw, 1953b).

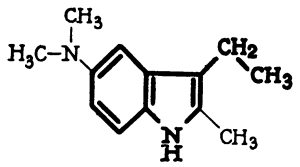

FIG. 2.—Structure of medmain.

Three classes of naturally occurring alkaloidal drugs were then recognized to be structurally related to serotonin, and were shown to be antagonized in their actions on smooth muscles by this hormone. These were the ergot alkaloids—for example, ergotoxine, ergotamine (Woolley and Shaw, 1953c; Shaw and Woolley, 1953; Fingl and Gaddum, 1953), lysergic acid diethylamide (Gaddum *et al.*, 1953)—the harmala alkaloids, such as harmine, or harmaline (Shaw and Woolley, 1953), and yohimbine (Shaw and Woolley, 1953). Structures of these compounds are shown in Fig. 3. Although these classes of alkaloids differ widely in chemical structure, they have in common an indole nucleus and a substituted aminoethyl side-chain which gives them all a resemblance to serotonin. They all act as competitive antagonists of serotonin on smooth muscles such as those in arteries.

They have a third feature in common. This is the ability of at least one member of each class to cause mental aberrations. Thus, the ergot alkaloid derivative lysergic acid diethylamide produces in man a transient state resembling schizophrenia (Stoll, 1947; Fischer *et al.*, 1951; Rinkel *et al.*, 1952; Hoch *et al.*, 1952). The harmala alkaloids bearing a methoxyl group cause hallucinations, and so disturb the mental processes of dogs that behaviour becomes noticeably changed. Crude yohimbine has long been known as an aphrodisiac. It has been suggested (Woolley and Shaw, 1954) that these mental changes may be the result of an interference with the action of serotonin in the brain. The drugs would thus be pictured as acting in the brain in a way comparable to that in which they act on various smooth muscles.

If this suggestion is correct, then other types of antiserotonins should cause mental disturbances. As a matter of fact, some of them do. Thus, 1-hydrazinophthalazine has been reported to bring about psychiatric disease in a man treated with relatively large doses (Moser *et al.*, 1953). It will be remembered that Taylor *et al.* (1951) demonstrated an antagonism between this drug and serotonin, as measured by effects on the blood pressure of dogs. The simple synthetic analogue and antagonist of serotonin known as medmain (Shaw and Woolley, 1954) (Fig. 2) apparently exerts an effect on the central nervous system because it elicits profound convulsive fits in mice. No clinical experiences with this drug have been attempted.

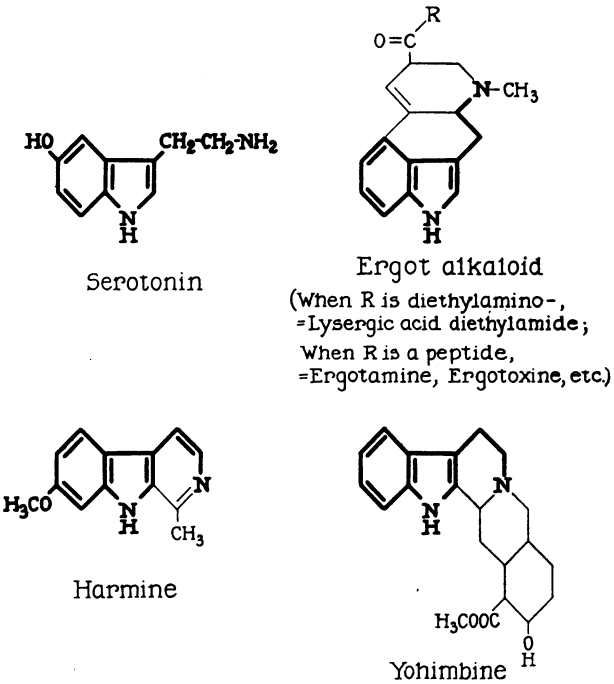

FIG. 3.—Serotonin and some naturally occurring psychogenic antiserotonins.

Do such findings permit one to conclude that the mental changes caused by the drugs are the result of an interference with serotonin? Two sets of experimental findings are against such a view. (*a*) Every antagonist of serotonin (as measured on smooth muscles) does not elicit the mental changes. Thus, although lysergic acid diethylamide does, ergotamine and ergotoxine do not. Medmain obviously affects the central nervous system of mice, producing convulsive fits, whereas 1-methylmedmain does not, even though it is equally potent as an antiserotonin on artery walls or uteri. (*b*) Serotonin should reverse the mental effects of the drugs. This has only been attempted in mice with medmain and with lysergic acid diethylamide, but in these cases serotonin failed to overcome the neurological effects of the drugs (Shaw and Woolley, 1954, and unpublished data). Clearly, the hormone can overcome the effects on smooth muscles, but not on the central nervous system.

In weighing this evidence one must remember the following points. Measurement of the increase in serotonin in the brain of a mouse injected peripherally with very large doses of this compound has shown that no detectable amount penetrated to the brain (Woolley and Shaw, 1954). Either the hormone did not find its way through the blood–brain barrier or else it was destroyed in the blood during transit to the brain. It is well known that the enzyme amine oxidase vigorously attacks serotonin, and that injected serotonin is rapidly cleared from the circulation. If serotonin itself finds difficulty in reaching the brain, then some of the antiserotonins may meet with similar difficulties. Presumably, only those antiserotonin drugs which penetrate to the proper place in the brain are able to cause the aberrations. This may aid in an understanding of why all compounds which antagonize the action of serotonin on smooth

muscles do not cause disturbances in the central nervous system. In any event, it seems clear that the direct introduction of serotonin, and of various antiserotonins, into the central nervous system will be needed if one is to settle this point.

Serotonin Deficiency

To Woolley and Shaw (1954) the findings with the drugs indicated that serotonin plays a part in the central nervous system in the maintenance of normal mental processes. The drugs may be pictured as acting by penetration to the brain and production there of a specific interference with these functions. A pharmacologically induced cerebral serotonin deficiency would thus be the cause of their psychotic effects—for example, the schizophrenia-like condition evoked by lysergic acid diethylamide. They have suggested that, if this view is correct, then naturally occurring psychiatric states such as schizophrenia might well be pictured as resulting from a deficiency of serotonin in the brain, brought about not by drugs but by failure of the metabolic processes which normally synthesize or destroy this hormone there. If this interpretation is correct, the trial of serotonin in practice for the treatment of these naturally occurring diseases would be suggested. However, because of the anticipated failure of peripherally administered serotonin to penetrate into the brain, it may be necessary to devise compounds with serotonin-like activity which can so penetrate.

It must be remembered that this opinion about a cerebral serotonin deficiency as the cause of conditions such as schizophrenia is a working hypothesis. Although one can demonstrate in smooth muscles a competitive antagonism between serotonin and the various drugs just discussed, there are other explanations which can be put forward for their psychotic effects. One of these is that the mental aberrations arise from an excess of serotonin rather than from a deficiency. Drugs such as the ergot alkaloids have been observed to cause inhibition of the enzyme amine oxidase (Orzechowski, 1941). This enzyme has been found in several tissues, including those of the nervous system (cf. Blaschko, 1952). It appears to be remarkably well constructed for the destruction of serotonin, although it will attack other amines such as adrenaline in a less vigorous fashion. If the amine oxidase of the brain were inhibited *in vivo*, as it is *in vitro*, by drugs such as have just been discussed, then an excess of the hormone would probably accumulate. The interference of these antiserotonin drugs would still be a consequence of their structural resemblance to serotonin. The difference would be that the competition with the hormone would be for the destructive functional site—that is, the enzyme amine oxidase—rather than for sites of action in the brain akin to those involved in the contractions of smooth muscles. Nevertheless, if cerebral amine oxidase were the chief serotonin receptor to be affected by the drugs in the brain, the result would be an excess of serotonin there, rather than a deficiency. In both situations the drugs would be acting as antimetabolites of serotonin, but the end-results would be quite different. In one case a deficiency and in the other an excess would appear.

Feldberg and Sherwood (1954) have quite recently provided experimental evidence of the behavioural effects of an excess of serotonin in the brain, and their results might tend to favour the hypothesis that the drugs act *in vivo* by allowing the accumulation of serotonin. In a cat provided with a permanently affixed cannula to facilitate painless injections into the lateral ventricle of the brain, Feldberg and Sherwood observed that the introduction of 100–200 μg. of serotonin resulted in several behavioural changes in the animal. These might be interpreted as being similar to some of the signs of clinical schizophrenia. For example, the lassitude and the willingness of the cat to remain in unnatural positions when so manœuvred by the experimenter might be likened to the catatonia seen in some human mental disorders.

It is clear that quantitative measurements of the serotonin levels in the cerebral fluids of mentally deranged patients, and of normal subjects, would be of much assistance at this time. The introduction of serotonin into the central nervous system of normal humans might also throw light on this problem, but the dangers of such an experiment are so plain that this course should not be pursued. It is one thing to administer the hormone peripherally, where it has been given to humans without serious consequences (Page and McCubbin, 1953; Reid, 1952), but it is quite another to introduce it directly into the central nervous system. Apart from these direct experiments, it would be well to know whether amine oxidase is in fact inhibited by each and every one of the drugs under discussion. The answer would help in choosing between the alternative hypotheses of deficiency or excess of serotonin as a causal factor in the aberrations.

If it should turn out that the accumulation of serotonin is the real difficulty in the drug-induced mental disorders, one might picture the naturally occurring diseases as arising from an excess of serotonin brought about by increased production or diminished rate of destruction. It would be possible to envisage the treatment of such a situation by the use of antimetabolites of serotonin so constructed as to be able to penetrate into the brain and not to interfere with the action of amine oxidase. Such compounds would exclude the excess serotonin from the postulated receptor sites which account for its functioning on nervous tissue. To envisage such an antimetabolite capable of inhibiting the action at the receptor site and yet not capable of inhibiting the normal destructive process for the hormone would be no different from the known situation with regard to acetylcholine. In that case drugs such as eserine inhibit the normal destructive process (choline esterase), whereas atropine and the curare-like agents introduce a block at the receptor site. There are now available antimetabolites of serotonin which have been shown to penetrate into the brain—for example, 1-methylmedmain (Shaw and Woolley, 1954).

A further objection to all of these points of view could be raised—namely, that the pharmacological and biochemical evidence is insufficient to justify any connexion of serotonin with the neurological effects. This point of view cannot be excluded. However, the combined evidence, both biochemical and pharmacological, seems to be sufficient to encourage pursuit of the working hypothesis that this hormone-like compound plays an important part in the functioning of the nervous system.

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THE MANAGEMENT OF HAEMOLYTIC DISEASE OF THE NEWBORN

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Haemolytic disease of the newborn can be predicted with certainty before delivery. The diagnosis can be established within minutes of birth, and with the use of exchange transfusion the mortality need only be of the order of 2% of live-born infants with this disease. Yet in England and Wales during 1952 the recorded mortality was 14%. This represents a loss of 435 lives in the year, but we believe that 367 of these infants might have been saved. This needless loss of a life each day constitutes a challenge we must not ignore.

Experience in the Northern Region, 1952–3

The purpose of this article is to describe our recent experience of this disease in the Northern Region, to serve as a basis for comparison. We deal mainly with 1952 and 1953 because it was only in late 1951 that spontaneous delivery and exchange transfusion was proved to be the treatment of choice for infants with this disease.

The management of haemolytic disease of the newborn in this region is based on the following facts, some of which are generally accepted, while others have emerged from our experience during the past six years: (1) At least 5 out of every 1,000 babies in the North of England will suffer from haemolytic disease of the newborn. (2) Of 100 such babies 10–15 will be stillborn. (3) Of 100 live-born babies with this disease, 60 will require transfusion sooner or later, while the remaining 40, being affected to a lesser degree, will survive without treatment. (4) For those requiring treatment, early exchange transfusion is superior to simple transfusion (Mollison and Walker, 1952). (5) Premature induction has no routine place in the management of this condition (Mollison and Walker, 1952).

Although blood-grouping tests will enable practically 100% of cases to be predicted antenatally, there are no reliable means of forecasting severity; therefore hospital delivery has been offered to all immunized Rh-negative mothers. Three outlying hospitals have provided for their immediate areas, while the Newcastle group of hospitals has provided for the remainder.

Points Considered

We have tried to judge the adequacy of the arrangements by considering the following points: (1) The number of cases of the disease predicted in relation to the number expected, which affords a measure of the completeness of antenatal supervision. (2) The selection of cases for treatment, on which will depend the ultimate prognosis for the affected infant. (3) The survival rate in affected babies, by which we may judge the efficiency of treatment.

Incidence

The variations in the incidence of haemolytic disease of the newborn in 1952 and 1953 are shown in Table I. In each year 25 of the expected 27 stillbirths were recognized. Table II shows that, as serological facilities become more generally used, so the incidence of haemolytic disease of the newborn apparently rises.

TABLE I.—*Variations in Incidence of Haemolytic Disease of the Newborn*, 1952–3

Area	Year	Total Births	Expected No. H.D.N.*	H.D.N. Diagnosed	Cases not Predicted		Incidence per 1000 Total Births
					No	%	
Northumberland	1952	13,399	67	73	—	—	5·4
	1953	15,022	75	61	14	19	4·0
Durham	1952	26,532	133	99	34	25	3·7
	1953	25,748	132	139	—	—	5·2
Cumberland† ..	1952	4,977	25	13	12	48	2·6
	1953	4,960	25	18	7	28	3·6
North Riding ..	1952	9,292	46	17	29	63	1·8
	1953	8,849	44	31	13	30	3·5

*Expected number of cases of haemolytic disease of the newborn calculated on an incidence of 5 out of every 1,000 total births.
†Although part of Westmorland comes within the Northern Region, there is a tendency for cases to drain to hospitals outside this region; we have felt that any figures for this county could not be representative, and have therefore excluded them.

TABLE II.—*Variations in Incidence of Haemolytic Disease of the Newborn Per 1,000 Total Births*, 1948–53

Area	1948	1949	1950	1952	1953
Northumberland	3·5	4·7	5·8	5·4	4·0
Durham	1·6	2·5	3·5	3·7	5·2
North Riding	0·4	1·7	1·5	1·8	3·5
Cumberland	0·75	2·1	1·7	2·6	3·6

In 1952 75 cases were missed, while 34 were missed in 1953. We assume that, although some of these infants would be stillborn and others so mildly affected as to require no treatment, lives have been lost unnecessarily.

Unfortunately, only 75% of cases in 1953 were predicted antenatally, the remaining 25% being diagnosed only after delivery. Of the 49 Northumberland and Durham cases not predicted, 42 were because of failure to test for antibodies between the 32nd and the 36th week of pregnancy. Technical error and the presence of rare antibodies accounted for only four and three cases respectively. Unaccountably, a number of mothers had been tested in one or more previous pregnancies, yet not in the current one.

Northumberland and Durham

Northumberland and Durham (including Newcastle and Tyneside, but excluding Sunderland and Stockton) are regarded as one area because in the two years under review all women resident here and found by routine antenatal tests to be "Rh-negative with antibodies" were offered delivery in one of the Newcastle group of hospitals. In each year four mothers, although living in the North Riding of Yorkshire, were delivered in a Newcastle hospital, and these cases are considered here.

Method of Treatment.—Where treatment was indicated we have used exchange transfusion, performed within nine hours of birth. By the umbilical vein route we have aimed to exchange 80 ml. per lb. (176 ml. per kg.) body weight,