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Some Recent Research on the Heart and Circulation

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A BRANCH of physiology which has recently had much attention is fœtal physiology. In choosing to start with the fœtus, then, it is because it is convenient to do so, though I cannot deny that I am proud to say that the work formed the subject of the John Mallet Purser Lecture, Trinity College, Dublin, given last year by my father.[1]

The fœtuses used for the investigations were lambs or kids of known intrauterine age. They were removed from the mother by Cæsarean section. A very important point was that after delivery they were placed in a bath of warm saline and the cord was not tied. For this reason the fœtus continued to get its oxygen from the placental circulation and did not breathe. At any desired moment it could be "born" by tying the cord; breathing ensued after a pause of rather less than a minute. At the risk of too much digression, I might mention that the essential stimulus for fœtal respiration was found to be oxygen lack; carbon dioxide accumulation, per se, was ineffective.

FŒTAL BLOOD-PRESSURE.

The following data may be taken as typical of the carotid arterial pressure of fœtal sheep of different intrauterine ages, full term in the sheep being about 140 days :—

Fœtal age in days - - -	49	101	120	123	137	138	140
Carotid arterial pressure in mm. Hg.	20	34	46	50	72	68	76

During the last six weeks of pregnancy the fœtal arterial pressure was doubled. The arterial pressure at full term, about 75 mm. Hg., is, however, very different from that of the new-born lamb. After "birth," that is, ligature of the cord, the pressure rises another 20 mm. Hg. at about the same time as breathing starts, so the pressure in the new-born lamb is about 100 mm. Hg. It is interesting to observe that the stage of development of the blood-pressure at birth is more advanced in

the lamb than in the baby. Bowman's[2] readings of a baby's systolic pressure on the first four days of its life are 55, 60, 60, 60 mm. Hg. respectively.

The Path of the Fœtal Blood-Stream.

The anatomists have given us the classical picture of the path taken by the fœtal blood-stream. They have deduced the course of the stream from the colour of the blood in the main blood-vessels. Red arterial blood from the placenta enters the right auricle, passes through the foramen ovale, and is propelled by the left ventricle through the carotids round the upper part of the body. Blue venous blood returning from the upper part of the body enters the right ventricle, and is propelled through the pulmonary artery and ductus arteriosus down the thoracic aorta into the trunk and placenta. These conclusions were tested by my father on the fœtal sheep.

At the chief points at which two tributary streams converged to form a main stream, and at which a main stream divided to form two tributary streams, the amount of oxygen in the blood of both the main stream and its tributaries was measured. By comparing the composition of the three streams, the relative rates of the streams in the tributaries could be determined. The results, which I quote verbatim from the Purser Lecture, were as follows :—

"1. The blood which passes through the heart may be regarded as forming two streams approximately equal in volume.

"2. One of these goes to the 'head,' and is not much inferior in its oxygen content to the redder blood which reaches the heart; namely, that coming along the inferior vena cava.

"3. The second, which is not much redder than the venous blood from the 'head,' goes to the 'body,' which means the lower part of the trunk and placenta.

"4. Of the blood going to the 'body,' about two-thirds goes to the placenta."

Actual measurement, therefore, confirms the deductions drawn from inspection.

There is a further interesting implication. It will be seen from the conclusions above that the blood-stream is divided among the chief territories of the fœtal circulation in the following proportions: "head," three-sixths; placenta, two-sixths; "body," one-sixth. In other words, the head or upper part of the body receives three times as much blood as the "body." A more exact idea of the territory supplied by the vessels of the "head" was obtained by ligaturing the aorta distal to the ductus arteriosus and injecting a dye into the left ventricle. "As well as the actual head and arms, the whole of the chest-wall was injected, and, what was very interesting, the coverings of the spinal cord, down almost to the lumbar swelling. Thus all the organs which at this stage of fœtal life are functionally important, except the liver and lowest section of the cord, can receive reddish blood from the upper circulation."

The Closing of the Ductus Arteriosus.

The effectiveness of the normal type of respiration which establishes itself at birth depends upon the rapidity with which the circulation changes from the fœtal

to the normal. This change involves the closing of the ductus arteriosus. The patency of the ductus arteriosus was investigated before and after "birth." Whereas it was wide open before tying the cord, it was found to be tightly closed a short time after. The mechanism for closing the ductus rapidly is not yet plain. It is true, however, that the histology of the ductus is quite different from that of the neighbouring blood-vessels—its walls are much more muscular.

The patency of the ductus arteriosus before birth implies that the right and left intraventricular pressure must be much the same, approximately 75 mm. Hg. This means that the fœtal right ventricular pressure is about 50 mm. higher than that of the adult.

The Cardiac Output in Man.

The "cardiac output" may be defined as the volume of blood ejected from the left ventricle in one minute. It is an index of the function of the heart, which is to supply blood to the periphery. The "acetylene" method, introduced by Grollman,[3] has recently been used for measuring the human cardiac output in a very wide range of physiological, pharmacological, and pathological conditions.

The principle of the method is briefly as follows. The volume of oxygen absorbed in the lungs in one minute (*a*), divided by the volume of oxygen which leaves one litre of blood in the peripheral circulation (*b*), gives the number of litres of blood transversing the lungs in a minute, that is, the cardiac output. The oxygen intake (*a*) is found by one of the methods ordinarily used for B.M.R. determinations. The "arterio-venous oxygen difference" (*b*) can be calculated from analyses of a mixture of air and acetylene which the subject rebreathes from a rubber bag. In practice the method is valuable, because the subject needs no training, and the measurements and calculation take only a few minutes. The author states that the method has an error of less than ten per cent.

Further remarks on the cardiac output under a variety of conditions may well be prefaced by saying that for a given individual, under basal conditions, the values are surprisingly constant. Over a period of nearly two years, determinations were done on a healthy young man about ten minutes after waking up and before getting out of bed. The average cardiac output was 3.9 $\pm$ 0.02 litres per minute (maximum variations). In this man the extreme variations in the cardiac output amounted to about six per cent.; the variation in his basal pulse, taken at the same time, was thirteen per cent.

Mild Exercise and Massage.

The effect of exercise on the cardiac output has been the subject of numerous investigations. The findings, in general, have pointed to the fact that the cardiac output is proportional to the oxygen consumption. Grollman's interesting experiments on the cardiac output in mild exercise throw a new light on the subject. The nature of the exercises and the oxygen consumption and cardiac output findings are shown in the following table :—

Experiment No.	*Exercise*	*Oxygen consumption in c.c. per minute*	*Cardiac output in litres per minute*
1	Resting - - - - -	246	4.1
2	Flexing and extending right forearm once per second - - - -	286	4.8
3	Alternately flexing and extending both forearms, each every other second -	315	4.3
4	Flexing right thigh once per second -	430	7.7
5	Alternately flexing both thighs each every other second - - - -	428	5.0

In experiments 2 and 3 the same number of "forearm bends" were done in a minute. The cardiac output, however, was greatest when all the bends were done with the same forearm. The oxygen consumption was greater when both forearms were used. The "leg-bend" exercises show the same thing, namely, that a given number of bends in a minute increase the output more if done with one leg than with two. The oxygen consumption was practically the same whichever way the leg exercises were done. One sees that in these experiments the cardiac output is more closely related to the rapidity with which groups of muscles are moved than to the oxygen consumption. A muscular contraction squeezes the blood towards the heart; on relaxation reflux is prevented by the valves in the veins. Rapid contraction increases the efficiency of this muscle "pump."

These results throw some light on the vascular effects of massage and passive movements. Liljestrand and Stenstrom found the oxygen consumption of one subject increased from 261 to 322 c.c. during massage of the shoulder muscles, to 285 c.c. during abdominal massage, and to 379 c.c. during passive movements. Does the cardiac output follow the increase in oxygen consumption? Pap found that there was no increase in the circulation in a massaged area, unless it was congested. In the light of Grollman's experiments on mild exercise, this could be explained by the reasonable supposition that massage does not return the blood to the heart nearly as effectively as natural muscular contraction; increased oxygen consumption, per se, is not a reliable index of increased flow. Further work on the cardiac output before and after massage will be valuable.

Baths and Heart-"Strain."

It is generally recognized that very hot baths are bad for invalids. It is interesting to see that the temperature of the bath water has a considerable effect on the cardiac output. Cold baths depress the output, but in some people hot baths may increase it by over three hundred per cent., an increase which would put more strain on the heart than other demands incurred in everyday invalid life such as meals, excitement, and mild exercise. Bath temperatures and cardiac outputs are shown in the following table:—

Experiment No.	*Temperature of bath, in degrees Centigrade*	*Cardiac output in litres per minute*
1	32.5	3.20 (before bath)
		6.93 (during bath)
2	38.0	3.76 (before bath)
		12.50 (during bath)
3	38.5	3.60 (before bath)
		5.69 (during bath)
4	22.5	3.06 (before bath)
		2.81 (during bath)

Insulin and Cardiac Output.

Several clinicians have called attention to the occurrence of circulatory shock and even death from heart failure during insulin hypoglycæmia. Ernstene and Altschule injected forty to eighty units of insulin into sixteen normal subjects, aged between 16 and 45; they noted the effect of the injection on the cardiac output. In all cases the output was increased. The increase varied from three to eighty-six per cent., with an average of twenty-nine per cent. Grollman draws attention to the danger of large doses of insulin, likely to produce hypoglyæmia, in cardiac cases.

Cardiac Output and Digitalis.

In agreement with Lundsgaard, Grollman finds that the cardiac output in valvular disease of the heart is diminished when signs of failure are present. The diminution may be up to fifty per cent., depending on the degree of failure. The "acetylene" method has been used by Stewart and his co-workers to assess the value of digitalis therapy in heart cases. As heart failure leads to a diminution in cardiac output, which in its turn leads to the manifestation of the signs of heart failure in the other organs, cardiac output measurements are the most important pharmacological index of the value of therapeutic agents in heart-disease.

The effect of digitalis (0.8-1.0 gram of digitan) was first tried on normal people. After four hours there was a *decrease* in the cardiac output, which was greatest after twenty-four hours and had disappeared after forty-eight hours. The pulse and area of the heart by X-ray were also decreased, and one subject experienced dyspnœa and cardiac pain on slight exertion. In normal subjects, therefore, digitalis puts the circulation at a disadvantage.

Quite the opposite findings occurred in cases of heart failure. "Thus in one patient with heart failure of the congestive type, and a clinical diagnosis of generalized arterio-sclerosis, hypertension, rheumatic heart-disease (mitral insufficiency), and cardiac hypertrophy, the cardiac output in the basal resting condition was 2.88 litres per minute, which corresponds to an abnormally low cardiac index* as occurs in heart failure. The cardiac area was 198.3 sq. cm. Administration of digitalis (1.0 gram of digitan) resulted in an increase in the cardiac output to 3.54 litres per minute, a decrease in cardiac area to 180.2 sq. cm., a slowing of the pulse, and

* Cardiac output per square metre of surface area.

alterations in the form of the T-wave of the electro-cardiogram. As the effects of digitalis wore off, the signs of heart failure reappeared, accompanied by a decrease in the cardiac output in the course of two weeks to 2.62 litres, and an increase in the cardiac area to 193.6 sq. cm. When digitalis was administered a second time, results similar to those first observed were obtained." It appears from these results that digitalis is only of value in heart failure; in the absence of failure it may even be contra-indicated. I believe it is correct to say that is in accordance with clinical experience.

The Mechanism of Digitalis Bradycardia.

This has recently been investigated by Heymans,[4] the leading authority on the physiology of the carotid sinus.

Dogs whose carotid sinus nerves are cut make a rapid recovery from the operation. They differ from normal animals, as they have chronic tachycardia and hypertension. The heart-rate in the normal dog is about ninety a minute; after denervation of the sinuses it is about 250. The normal and the sinus-denervated animals behave differently after the administration of the digitalis compounds. After an intravenous injection of 0.03 milligrams of ouabaine per kilo body-weight, the heart-rate of a typical normal dog fell from 100 to 64, a reduction of about forty per cent. In the denervated animals a typical effect of the same dose of ouabaine decreased the heart-rate from 270 to 260, a slowing only amounting to four per cent. Since denervation of the carotid sinuses almost abolished the digitalis bradycardia, Heymans seems fully justified in concluding that the bradycardia is due to the action of digitalis on the sinuses. According to his teaching, the heart-rate in normal animals is permanently kept in check by a reflex from the sinus; this reflex is due to the pressure of the blood upon sense-organs in the sinus walls. Heymans' view is that digitalis increases the sensitivity of the sinus sense-organs, and for this reason the normal blood-pressure elicits an exaggerated reflex inhibition of the heart.

The Pulse in Exercise.

I have already referred to the relationship between cardiac output and oxygen consumption in exercise. This section describes some recent work on physiology of the heart-rate during activity.

Muscular work and increase in the pulse are always associated with each other. This partnership invites the conclusion that increase in the pulse is necessary for the proper function of the heart in exercise. Although it is true that cardiac output may be increased from three to as much as thirty litres per minute—is the increase in the pulse essential? A second question of interest is the cause of the increase in the pulse; so many factors are known to affect the heart-rate that the relevant ones and their comparative importance are not obvious. Experiments on these problems were done in Heymans' laboratory by Adli Samaan;[5] I was fortunate to be his colleague in another investigation at University College.

Samaan's scheme was to count the increase in the pulse in normal dogs in exercise, and then to repeat the observations after cutting one or more of the nerves which might be causing tachycardia.

The type of exercise was carefully controlled. Each dog had its own "standard exercise," and also did a "maximum endurance test." Both exercises were done in a treadmill driven at a constant speed. The "standard exercise" lasted double the time which elapsed before panting began. In the "maximum endurance test" the dog ran on the treadmill until it was tired; the duration of running was expressed in multiples of its "standard exercise" time. In every case the heart-rate was recorded at rest and just before the end of the exercise. An electro-cardiographic method was used. Typical results are shown in the following table :—

Series	*Operation*	*Resting Pulse*	*Pulse at end of standard exercise*	*Increase in pulse during exercise*	*Maximum endurance in multiples of standard exercise time*
1	Normal dogs - - -	90	230	140	3
2	Vagotomy or atropine - -	200	280	80	1
3	Cardiac sympathectomy -	70	140	70	8
4	Suprerenal glands denervated -	90	170	80	3
5	Vagotomy or atropine, cardiac sympathectomy, suprarenal glands denervated - -	120	130	10	2
6	Vagotomy or atropine, suprarenal glands denervated -	185	210	25	1

In the first place, the experiments show the very strong tonic influence of both the vagus and sympathetic on the resting heart. The natural resting rhythm of the S.A. node in the denervated heart (series 5) is about 120 per minute. With vagi cut but sympathetic intact (series 2) it is 200. It is the imposition of very strong vagal tone which brings the pulse down to 90 in normal resting dogs (series 1).

The table also shows that the following three factors contribute to the acceleration of the pulse in exercise :—

1. The vagus nerve. After vagotomy the increase in the pulse in exercise was reduced from 140 to 80 (series 2).
2. The sympathetic supply to the heart. After sympathectomy the increase in the pulse was reduced to 70 (series 3).
3. The secretion of adrenaline. After denervation of the suprarenals the increase in the pulse in exercise was reduced to 80 (series 4).

This is confirmed by the fact that after complete denervation of the heart and suprarenals, exercise produces a negligible increase in the pulse, only ten beats (series 5). This slight increase may be explained by the rise in temperature of the blood acting directly on the S.A. node.

The most important factor in the increase in the pulse in exercise is the removal of the vagal tone, which allows the sympathetic tone full play. The increase in sympathetic tone in exercise is surprisingly slight, as can be seen in series 6, after vagotomy and denervation of the suprarenals. In these animals the acceleration of the pulse in exercise could only be due to excitation of the heart by increased sympathetic tone, and the acceleration only amounted to twenty-five beats per

minute. The secretion of adrenaline also plays a definite but subsidiary rôle in quickening the heart.

The maximum endurance test has a point of remarkable interest. It will be seen that the normal dogs could run for three times the duration of their standard exercise before the onset of fatigue. The dogs with the sympathetic supply to their hearts cut (series 3) could last out *eight* times the duration of their standard exercise. This means that a dog with a cardiac sympathectomy has nearly three times the endurance of a normal dog. Does this mean that a gold mine is waiting for the owner of a stud of sympathectomized racehorses? On the other hand, vagotomy reduces the maximum endurance: the dogs are "done" at the end of the standard exercise. It is very difficult to see why sympathectomy and vagotomy should have these effects. It does not seem to be due to their influence on the heart-rate. A. V. Hill has shown that the limiting factor in the duration of exercise in man is the cardiac output, which, in its turn, is limited by the oxygen supply of the heart. As the sympathetic nerve conveys dilator impulses to the coronary vessels, one might suppose that section would prevent full coronary dilatation in exercise, and so limit the cardiac output and maximum endurance. In point of fact, sympathectomy has a beneficial effect. Further inquiry into this paradox will be valuable.

Lastly, the normal tachycardia of 230 in exercise does not seem to be necessary for the proper execution of the exercise. In the sympathectomized dogs the pulse was only 140, yet they had a greater capacity for exercise than normal dogs.

Metabolism of the Heart.

This problem of great physiological interest is beset with practical difficulties. Recently much valuable progress has been made by A. J. Clark,[6] at present external examiner in pharmacology at Queen's University. Much is already known about the metabolism of skeletal muscle; Clark's work has illuminated certain similarities and differences in that of cardiac muscle. Owing to the difficulty of experimenting with mammalian hearts, Clark's work was done with frog and tortoise hearts.

The salient points of the metabolism of a skeletal muscle during contraction are shown in the following equations:—

$$\text{Phosphagen} = \text{phosphoric acid} + \text{creatine}$$
(energy for contractile process).

$$\text{Glycogen} = \text{lactic acid}$$
(energy for phosphagen resynthesis).

$$O_2 + \text{lactic acid} = CO_2 + H_2O$$
(energy for resynthesis of four-fifths lactic acid).

The energy for a contraction is set free by the breakdown of some of a small store of phosphagen. This is followed almost at once by the breakdown of a little of the large store of glycogen to lactic acid. The formation of lactic acid releases energy which is used for the immediate resynthesis of the phosphagen. When oxygen is available, as it normally is, one-fifth of the lactic acid is oxidized to CO_2 and water; the large amount of energy liberated by this oxidization is used to resynthesize the remaining four-fifths of lactic acid to glycogen.

Under "anærobic" conditions, fatigue sets in sooner, but a great number of contractions can still be carried out; the phosphagen cycle and the breakdown of glycogen to lactic acid go on as usual, but the lactic acid cannot be resynthesized.

When muscle is poisoned with iodoacetic acid, lactic acid formation is stopped; only a few contractions are possible, as the small store of phosphagen is soon broken down and cannot be restored in the absence of lactic acid formation.

One of Clark's important discoveries is that the energy for the contractile process of heart-muscle is, like that of skeletal muscle, derived from the breakdown of phosphagen. A minor point of difference between the two types of muscle is that when skeletal muscle is active a little of the phosphoric acid and creatine escape into the blood; under similar conditions no phosphoric acid escapes from the heart. As regards phosphagen, then, the main thing is that in both types of muscle it supplies the energy for the contraction itself.

Under anærobic conditions the frog's heart may go on beating for many hours. There is a loss of glycogen from the muscle, and lactic acid is formed. Glucose added to the perfusion fluid is taken up by the heart and used for lactic acid formation. If iodoacetic acid is added to the perfusion fluid (anærobic) the heart stops in a few beats, because lactic acid cannot be formed, and so phosphagen cannot be resynthesized. One may go as far as to say that under *anærobic* conditions the metabolism of heart and skeletal muscle is much the same. Both derive the energy for phosphagen resynthesis from one and the same reaction—the breakdown of glycogen to lactic acid.

The "ærobic," and hence the normal, metabolism of heart and skeletal muscle differ. Iodoacetic acid stops skeletal, but not cardiac muscular contraction. This substance, as previously mentioned, prevents the formation of lactic acid from glycogen. The implication is that under *ærobic* conditions the heart is not dependent on the breakdown of its glycogen for the provision of energy for phosphagen resynthesis: the energy can be drawn from another source, not available in skeletal muscle. It is naturally very important to know if glycogen metabolism plays any significant part in the normal heart. According to Clark, only about forty per cent. of the oxygen used by the ærobic heart may be regarded as taking part in the oxidization of carbohydrate. Thirty-six per cent. of the oxygen consumption provides energy by combusting protein; the remainder combusts some unknown material, which, however, is not fat. Further important developments may be expected in this field.

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The Pharmacology of the Digitalis Drugs

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A SUMMARY of the actions of these drugs involves a survey of well-established conclusions and a critical examination of contrary opinions. Although experiments which appear to give opposite results are often in fact not comparable because of differences in technique, contradictions sometimes occur when such differences are not apparent; and, in that case, reference to individual papers is hardly possible without reference to all. Completeness of outline is thus prevented by the futility of trying, with limited space, to give a fair presentation of evidence in controversial matters.

SOURCES AND NATURE.

Many plants of different natural orders contain poisonous principles with a similar characteristic action on the heart, and some of them have been used by uncivilized races as arrow-poisons, or for trial by ordeal. The active substances in such plants are nearly all chemically related glucosides, several of which are often found in the same plant. These drugs form the digitalis group, though only a few of them have yet obtained a firm foothold in medicine. A number of animal products also have a digitalis-like effect, but are not of therapeutic importance; while calcium and barium have actions on the heart which resemble in some respects the action of digitalis.

Great difficulty has been experienced in separating and purifying the various glucosides, but some have now been isolated and others at least identified as definite substances. The chief glucosides of therapeutic interest are included in the following list :—

Digitalis purpurea.	*Digitalis lanata*	*Strophanthus*	*Squill*
Digitoxin, Gitalin, Gitoxin (from the leaves)	Digoxin	k-Strophanthin	Scillaren A
Digitalin (from the seeds)	Digilanid A	g-Strophanthin	Scillaren B
	Digilanid B		
	Digilanid C		
	Gitoxin		

The actions of these substances resemble each other closely. They differ in quantitative and time relations, but not in essential character. The glucosides are extremely poisonous. Their unusual toxicity would be much more apparent if they could reach the heart without loss. Digitoxin appears to be the most active of the D. purpurea group (Nativelle's digitalin is probably digitoxin), and the lanata glucosides are perhaps rather more powerful. The glucosides of squill (especially scillaren B) are more powerful than those of digitalis, and the strophanthus group have, in general, about the same activity as those of squill.

The lethal dose of these glucosides is much greater when given orally than when given by intravenous injection. Part of the drug is destroyed in the alimentary canal—probably more in the stomach than in the intestine—and part may be fixed by the liver, although this is somewhat doubtful. But loss of activity is due chiefly to slowness of absorption, typical of the group, which is in striking contrast to the rapid absorption of alkaloids. Strophanthin is absorbed even more slowly than digitoxin, and this explains the uncertainty of its action when preparations containing it are taken by mouth.

> Pardee[8] found that when digitalis tincture was given in a dose of one minim per pound body-weight, the earliest electro-cardiographic sign of an action appeared in two to four hours. The maximum effect was reached in six to seven hours, and seemed to be maintained for twenty-four hours.

When the glucosides are injected they disappear quickly from the blood, not because they are destroyed, but probably because they are taken up by the tissues. The quantitative distribution in various tissues has not been finally established. The heart seems to have the greatest retaining power, the abdominal organs less, and the lungs none. The skeletal muscles are much inferior in this respect to the abdominal organs, but low specific fixation is more than compensated by their preponderance in the body. Weese[11] thinks that the glucosides may pass but once through the coronary circulation, because the blood may be cleared of them before it can return, and may contain, therefore, only freshly absorbed glucoside. This is not true when toxic amounts are given, and probably not even for therapeutic dosage, but it may be near enough the truth to indicate how small a proportion of the total dose has a chance of affecting the heart. And, in any case, only about ten per cent. of the whole circulation goes through the coronary arteries, so that much of the drug can be fixed by the tissues without reaching the heart-muscle at all.

The glucosides are slowly destroyed in the body, though there seems to be no direct evidence that any organ is specially concerned with their destruction. Traces are excreted by the intestine and kidneys, but excretion plays a subordinate part in their removal. A relatively large amount may reach the intestine in the bile, but, if so, the greater part of this is reabsorbed.

The duration of the effect of a single dose, and the possibility of accumulation when doses are repeated, will depend on the balance between rate of removal from the body and rate of absorption, and, in particular, on the tenacity with which the drug is retained by the heart-muscle. The digitalis glucosides accumulate more than those of strophanthus or squill, and the lanata glucosides do not seem very different in this respect from digitoxin. But evidence favouring accumulation is derived chiefly from determinations of the percentage of the lethal dose still needed to cause the death of animals which have already, some days previously, been given a known percentage of the lethal dose; and recent observations suggest that this may be evidence of accumulation of injury and not of the glucosides. Thus, three days after a toxic dose, areas of necrosis may appear in the heart-muscle, due,

perhaps, to a disturbance of the coronary circulation. The strength of the heart may be increased on the first or second day after digitalis has been given, but later there may be observed a progressive decline in the functional condition, which corresponds to the onset of morphological changes.[1, 2, 12] In therapeutics, however, accumulation of effect is more likely to depend on accumulation of the drug, and deductions from the pathological results of toxic dosage must be made with caution.

Clinical experience has shown that the heart is more sensitive to digitalis in disease than in health. Even when compensation has been established, increased sensitivity remains. And this is confirmed by animal experiments in which cardiac insufficiency has been produced.

No drug removes completely the effects of digitalis, though a few are partial antagonists (quinine, quinidine, etc.). Sympathomimetic drugs may increase the tendency to fibrillation. Stewart and Rogoff[9] found that irregularities caused by strophanthin disappeared when the outflow of suprarenal secretion was prevented, and appeared again when adrenaline entered the circulation.

There is no clear experimental evidence that digitalis protects the heart against either anæsthetics or bacterial toxins.

Action.

Rate.—The reduction of heart-rate with moderate doses of digitalis is prevented in mammals by section of the vagi, or by atropine. Action through the vagus has been attributed by Cushny[3] to direct stimulation of the vagal centre; by Straub[10] to an increase in the sensitivity of the heart to unaltered vagal impulses; by Hering,[5] Heymans,[6] and their co-workers to reflex vagal stimulation initiated in the carotid sinus by a rise of blood-pressure. The reflex theory is well supported by experimental work; and although in man a rise of blood-pressure is not observed with therapeutic dosage, it may in fact be abolished by the reflex which it causes. Only a small stimulus is needed, for the slowing of the pacemaker is not great, and the heart may be more sensitive to vagal stimuli, as Straub believes. The treatment of auricular fibrillation with digitalis results in a greater decrease of pulse-rate, which has, however, a different origin.

Tone and Contractility.—Moderate doses of the glucosides cause apparently an increase of tone and strength of contraction but, in health, no increase in the output of blood from the heart. The size of the heart-shadow is thus reduced and the displacement of the cardiac border more evident, while a fall in the circulation-rate often occurs. In cardiac disease the heart-shadow shows similar changes under digitalis, but these are more definite because dilatation is relieved. Either an increase or a decrease in circulation-rate may be observed, the result depending, perhaps, on the degree of cardiac failure that existed. More powerful contractions need not augment the output of blood, because, if the tone is greater, diastolic filling may be less complete; while extracardiac factors influence the return of

blood to the heart, and thus the amount that contraction can expel. And of some importance, also, is the observation that both in health and in cardiac disease, digitalis can lessen the actual quantity of circulating blood, probably by increasing storage in various reservoirs.

Wollheim[13] describes two types of decompensation. In one type (associated with hypertonus, aortic insufficiency, etc.) the amount of blood in the circulation is increased, and the effect of digitalis is beneficial. In the other, usually cyanotic, type (associated with pulmonary or mitral stenosis and other conditions) the circulating blood is reduced, and digitalis has an unfavourable effect.

The powerful contractions, however, enable the heart to empty itself more completely, so that, without changes in rate, venous flow, and arterial resistance, the same amount of blood may be expelled from a smaller cardiac volume.

Contraction is more rapid and the emptying time is shorter when therapeutic doses of digitalis have been given. The maximum intraventricular pressure is probably higher.

The increase in tone and in power of contraction is the result of a direct action of the glucosides on the muscle of the heart, and is not prevented by atropine or by vagal section. According to Cushny,[4] the normal heart often relaxes more completely under digitalis, but this is due to stimulation of the vagus and is not observed after atropine. Since the heart would thus contain more blood, the output per beat would be greater, even if the power of contraction were unaltered; a conclusion apparently not in harmony with more recent observations of the effects of therapeutic dosage in normal man. In any case, there seems to be general agreement that when the heart is dilated, the direct action of digitalis renders diastole less complete and so reduces the dilatation.

Conduction.—Conduction of impulses from the auricle to the ventricle is depressed by stimulation of the vagus. In mammals, if the heart is normal, digitalis acts on conduction through the vagus, and its effect is therefore removed by atropine, while very large amounts of the drug are needed for a direct action on the conducting fibres. In disease of the heart, however, and in certain experimental conditions, the glucosides appear to act directly on conduction, and atropine does not prevent the effect of therapeutic doses.

No other action of digitalis has so great importance in treatment. When auricular fibrillation occurs, very numerous and irregular impulses are generated in the auricle, and these cause frequent and irregular contractions of the ventricle. The filling time between the contractions is too short, and partial failure of the circulation results. If the conducting mechanism is depressed by digitalis, many auricular impulses never reach the ventricle, and a slower and more regular ventricular rhythm is established; while fibrillation of the auricle continues but does not involve circulatory failure.

In auricular flutter a similar partial block may be produced by digitalis, and the pulse become less frequent while the auricular rate is maintained. But often, under digitalis, the flutter passes into fibrillation, and if treatment is then stopped the auricle may resume its normal rhythm.

Irregularities caused by digitalis.—Sinus irregularities sometimes occur and affect the whole cardiac rhythm. They are due to an action through the vagus, and are removed by atropine.

The tendency to spontaneous contraction is increased, and extrasystolas may originate in any part of the cardiac muscle—more commonly, however, in the ventricle than in the auricle. One of the most frequent irregularities is bigeminal rhythm, in which each normal beat seems to arouse an autogenous beat, so that extrasystoles alternate with normal contractions. Very rarely auricular fibrillation has appeared in patients who had previously a regular rhythm.

Pulsus alternans is also a rare occurrence in treatment with digitalis. In animal experiments a similar condition is observed occasionally as an antecedent to partial block, but its significance is uncertain.

Depression of conductivity in the A-V bundle, though valuable in auricular fibrillation, may be objectionable in other disorders. Partial block is often at first of inhibitory origin, and can be relieved by atropine; but with higher dosage of digitalis a direct action on the conducting fibres may supervene.

Effect on the electro-cardiogram.—There is apparently no fixed relation between dosage and electro-cardiographic changes; great quantitative differences are observed, not only with different glucosides, but also in different individuals, although qualitatively the effects are similar. Whether these changes are the expression of a toxic or a therapeutic action seems doubtful. In some clinical investigations the P-R interval has been longer and the T-wave flattened or inverted, while other observations have revealed partial A-V block but no typical change in the T-wave. And in the normal human heart the T-wave may show no characteristic change, even with toxic dosage. The importance of vagal action cannot be denied, though Lagen and Sampson[7] have found that the electro-cardiogram of the chick embryo heart is affected in much the same way by digitalis, whether tested before or after the ingrowth of nerve-fibres.

Effects of toxic dosage on the mammalian heart.—Early results of toxic doses correspond to the therapeutic effects in man. The rate is reduced unless inhibitory impulses are prevented from reaching the heart; while the contractions are stronger, whether the vagi are cut or intact. Sometimes, at a later stage, inhibitory slowing becomes extreme, so that, even if each powerful systole expels more blood, the total output is not maintained. Conduction begins to fail and heart-block appears, at first partial, then complete, with separate auricular and ventricular rhythms. The spontaneity of the cardiac muscle is greatly exaggerated, and inhibitory control is lost. Extrasystoles may arise from any point in the heart, and the beats become more and more frequent and irregular, until the ventricle fibrillates and blood is no longer expelled.

Vomiting.—Vomiting is a clinical sign of overdosage with digitalis. Its occurrence is earlier with intravenous than with oral administration, and this has led to

the belief that it is induced by a central action. But, in contrast to apomorphine, the glucosides have no emetic effect when applied directly to the vomiting centre. These observations suggest that the stimulus is initiated at some peripheral point outside the stomach; and an action on the heart cannot be excluded as a possible cause of the reflex.

Diuresis.—In animal experiments often no diuresis is observed; but when water has been given previously, the glucosides may hasten its excretion and augment the output of chloride. Even when diuresis occurs, the renal blood-flow is seldom increased, though the oxygen consumption of the kidneys is greater.

Diuresis in cardiac œdema is attributed by Cushny[4] to the action on the heart. Because the circulation in all parts of the body is improved, fluid leaves the tissues to enter the capillaries, and the kidneys respond as usual to dilution of the blood. Cushny's view does not seem inconsistent with a decrease in the circulation-rate sometimes observed in recent experiments. For the essential result of successful treatment with digitalis is improvement in the circulation, however this may be revealed; and the advantage may well be derived from a fall in venous and capillary pressure, so that fluid can be drawn more readily from the tissues by the osmotic tension of the plasma colloids.

Against the cardiac origin of diuresis is clinical experience of differences in the diuretic effects of various glucosides, without corresponding differences in their effects on the heart. But, while other actions may be admitted as possible subsidiary factors, the relief of cardiac œdema must depend ultimately on the degree to which a normal circulation can be approached, and therefore on the success with which the function of the heart can be restored.

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Examination of the Heart in Childhood

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AT first glance it seems to be quite obvious that the diagnosis of heart-disease in the child is much more simple than in the adult, but this is not always true; it is certainly much more important, for the presence of a cardiac lesion in youth is of greater significance than in the old. The problem must be approached in three ways: first, by consideration of the patient's history; secondly, by inquiry into his symptoms; and thirdly, by comparison of the patient with the standards which our knowledge and experience have evolved as constituting the normal.

HISTORY.

During the first few years of life the child is exposed to many and varied forms of infection: against some of these he can mobilize racial or familial immunity; against others he must apparently fight his own battle. It is remarkable how few of these infections have any obvious effect on the heart—even syphilis only rarely in proportion to its effects on adult hearts. If, therefore, one can exclude rheumatism, one has gone a long way, but, to use an Americanism, juvenile rheumatism has a "sneaking" onset, and carditis may be its only demonstrable manifestation. The other infections with an affinity for the heart are scarlet fever and diphtheria. Congenital malformation, too, presents itself in many and diverse forms; those which are not associated with cyanosis are obviously the more difficult.

SYMPTOMS.

Children are more honest and more courageous than adults, and will state their symptoms without either additions or reservations, but they are prone to forget unpleasant things, and the memory of such symptoms as pain and breathlessness, once relieved, is blunted until they recur. Again, the onset of cardiac incapacity is insidious, and, in children, its main incidence occurs at an age when the child has scarcely formed for himself any standard of normal fitness, and therefore does not realize how far he has fallen below normal standards.

Adults with cardiac disease may be grouped broadly into those whose principal symptom is breathlessness and those whose complaint is pain, and the task of the physician may be described as an attempt to assess the degree and significance of these two disabilities. In the child as in the adult, BREATHLESSNESS is the cardinal symptom of congestive heart failure. The casual question, "Are you short of breath?" may be met by a perfectly honest denial; but when one asks a small boy who plays football in the street whether he is a forward or a back, and he replies that he is the "goalie," one will elicit a surprised negative to one's supplementary question, "Have you as much puff as some of the other lads?" This is because he has instinctively compromised between his longing to do as the others do, and his own limited capacity for exertion. (There are, however, many exceptions to the general rule that a child will avoid exercise which will do him harm.) The child

who has had cardiac dyspnœa for years often seems to have forgotten what it is like to breathe without effort, and, propped up on pillows, with orthopnœic cheerfulness will tell you that he's "fine, thanks." Similarly, a child seldoms complains spontaneously of PALPITATION, and many children seem to be unaware of even very rapid and forcible cardiac action. It is much more common for the mother to tell you that "his wee heart was just flying, doctor." The common causes of tachycardia in childhood are emotional disturbance, toxæmia, and carditis. The part played by the first-named is best assessed by counting the sleeping pulse-rate: when this is below ninety per minute it is said to afford evidence that a rheumatic toxæmia has subsided. Toxic goitre and true paroxysmal tachycardia are exceedingly rare before puberty.

PRÆCORDIAL PAIN, on the other hand, is a frequent symptom in rheumatic carditis: its presence should always make one suspect pericarditis even if a rub cannot be heard; one should remember first how much more frequently pericarditis is found post-mortem than by the bedside (Kerley[1] has said that pericardial effusion is more often missed than any other lesion); and, secondly, that pericarditis, especially with effusion, may be painless. In spite of this it is probable that gastric and intestinal distension may give rise to pain which is attributed to the heart.

COUGH is a common symptom, especially in later childhood, for the same causes as in adults, and with this additional cause, that rheumatism, or its associated tonsillitis, is an important cause of tracheo-bronchial adenitis. HÆMOPTYSIS is not, in my experience, a common occurrence in juvenile heart-disease; this is partly because mitral stenosis is rare before the age of ten years; but even in established mitral stenosis in children it is less common than in adults.

FAINTING ATTACKS are seldom caused by heart-disease: the common form is the vaso vagal attack, in which splanchnic dilatation is associated with vagal overaction and slowing of the heart-beat. Pain and emotional distress are the common determining causes. To these I would add prolonged standing: this used to be a common cause of fainting among students in wards. Perhaps the rising generation are of sterner stuff, or their teachers less long-winded, for it seems to be less common that it was. When organic heart-disease is associated with fainting attacks in childhood, the aortic valve is commonly incompetent. The syncopal attacks of heart-block (Stokes-Adams syndrome) are more common in adults. In children the possibility of epilepsy must always be borne in mind.

OEDEMA OF THE EXTREMITIES occurs less readily in the congestive heart failure of children than of adults, and ASCITES relatively more commonly. I suggest that this is because a child's limbs are more restless than an adult's, and thus the pumping action of muscular contraction on veins and lymphatics is more efficient. Therefore œdema of the extremities, when it occurs in children, is a more serious sign than in adults, and is more frequently part of a generalized anasarca.

Other signs of congestive heart failure are DISTENSION OF THE VEINS OF THE NECK AND ENLARGEMENT OF THE LIVER. The former is more easily determined than the latter: the pillows on the examination couch should be kept at a level which has been found not to cause filling of the veins in normal subjects; when the patient's

neck muscles are relaxed and his jugular veins are observed to be distended, this distension is due either to congestive heart failure or to obstruction of the great veins. "The liver, however, is an organ which varies greatly in size within the limits of health, so that it is impossible to define precisely the differences in its position at different periods of life" (Symington[3]). When one suspects that the liver is enlarged, subjective soreness and tenderness on pressure are confirmatory evidence of hepatic congestion.

The child with rheumatic heart-disease has been described by F. John Poynton[2] as the most alert and engaging of all our patients. Lassitude and fatigue are the earliest symptoms of cardiac disability in children. These two statements appear contradictory, and yet I believe that both are true. It is during the toxic stage that the child seems unwilling to leave the fireside and loses interest in the things he loved. Even before the "smouldering fire" of rheumatism dies down his interest in life is reawakened if he is placed at bodily rest in pleasant surroundings.

COMPARISON WITH NORMAL STANDARDS.

1. PULSE-RATE.—Edith M. Lincoln[4] has shown that there are slight differences in the pulse-rates of boys as compared with girls, and also in children lying as compared with standing. For general purposes it may be taken that the normal pulse-rate at rest is 100 per minute at three years, 90 at eight, and 80 at twelve years. These figures are, of course, very easily affected by many factors: a child whose pulse-rate is rapid at every out-patient visit may quickly settle down to a normal pulse-rate after a few days as an in-patient. The nature of a BRADYCARDIA is best determined by the electro-cardiograph. An abnormally slow pulse in infancy or childhood is in rare cases due to congenital heart-block, which may be associated with patent inter-ventricular septum. There is possibly a history of syncopal attacks. It should be noted that in congenital heart-block the ventricular rate is higher than in acquired dissociation of auricle from ventricle; Joseph Lewis[19] found the average rate forty-three per minute. Physiological bradycardia, with normal relationship of auricles and ventricles, rarely lowers the pulse-rate below sixty per minute. Over-dosage with digitalis must always be remembered as a cause of slow heart-rate and of coupled beats. PAROXYSMAL TACHYCARDIA may be due to a series of extrasystoles uninterrupted by any normal beats, or to periods of auricular flutter or auricular fibrillation. The exact nature of the increased rate can be determined in the majority of cases only by electro-cardiography, but in the last-named the pulse is irregular and the pulse-rate rarely rises above 150 per minute. Wilkinson[5] makes the interesting point that when the sequence of extra-systoles arises in the auricle or in the auriculo-ventricular node, the patient may suffer only slight inconvenience, while, on the other hand, ventricular extra-systolic tachycardia may be the cause of extreme discomfort, and occasionally may lead to syncopal attacks because of the ineffectual cardiac output and inadequate cerebral blood-supply.

2. BLOOD-PRESSURE.—A similar guide to the average range in the blood-pressure of children may be expressed as follows:—90/65 at three years, 100/70 at eight

years, 105/75 at twelve years. K. D. Wilkinson[5] says that a systolic pressure of 100 below the age of ten years may be regarded as pathological. Hypertension in a child is almost always associated with renal disease. "Essential" hypertension is very rare in childhood, although cases have been recorded by Craig,[6] Keith and Kernohan,[7] and others.

3. HEART-SIZE.—The determination of the size of the heart in a child is more difficult than, for example, in an adult male, for various reasons. First, percussion is even less reliable : this method has long been moribund and has recently been given its *coup-de-grâce* by John Parkinson,[8] who describes it as "a crude expedient in certain cases"; such cases, I take it, include gross enlargements and, in particular, pericarditic effusions where it may be of value in determining the right border of the dull area. Secondly, the standards of normal are more difficult to assess : Symington,[9] in "The Anatomy of the Child," wrote as follows : "Clinicians are divided as to the intercostal space in which the apex-beat is felt in children. Some hold that it is generally found in the fourth intercostal space, and they therefore assert that the heart lies higher in children than in adults; while others believe it to be as a rule in the fifth space. S. Gee found the heart lying high and the impulse in the fourth interspace in children under eleven years. Gierke examined fifty children whose ages varied from eight days to thirteen years, and found the apex-beat in the fifth intercostal space in thirty-eight of these, in the sixth in six of them, in the fourth in two, while in three it was behind the fourth ribs, and in one behind the sixth. . . . I have made a large number of frozen sections of the thorax in children of various ages, and I have failed to find any peculiarities in the height of the heart and great vessels in relation to the anterior chest-wall in them as compared with adults. It is known that the heart varies somewhat in position in different individuals, but in only one of my cases was the apex of the heart in the fourth interspace, while in several it reached the lower border of the sixth costal cartilage. . . . The heart appears to be relatively larger at birth than in the adult. Vierordt calculated that the heart was 0.89 per cent. of the whole body-weight in the new-born child, while in the adult it was only 0.52 per cent. In contrast with this it will be remembered that one of the characteristic features of the infantile thorax is its narrowness from side to side. Since the vertical extent of the heart in relation to the anterior chest-wall is practically similar in infants and adults, it will naturally follow that the transverse diameter of the heart as compared with the chest is relatively greater in the former than in the latter. This is very evident if a horizontal section of the thorax in an infant, at about the level of the fourth costal cartilages, be compared with at the same level in an adult. This greater breadth of the heart, as compared with that of the chest in an infant, naturally causes an extension outwards of the position of the apex-beat in relation to the nipple. Thus, in the adult, the apex-beat is normally about an inch internal to the mamillary line, while in children it is often directly below or even external to this line." Symington goes on to say that "clinicians appear to be tolerably well agreed on this subject." And yet I think that the point is too frequently overlooked and a diagnosis of dilated heart made too glibly; and the position of the apex-beat is not

by itself sufficient evidence of cardiac size. The heart is not a fixed organ, but an anchored pump, and its position is altered by various factors. The advent of X-rays has provided the best method of the estimation of cardiac size; as Parkinson[8] points out: "No organ is so well placed for X-ray inspection as the heart; it is surrounded by translucent lung, and by rotation of the patient can be viewed from every angle." This is particularly true in the case of the child, whose chest is smaller and more translucent, and whose heart is more easily studied through the fluorescent screen. To offset these advantages, certain difficulties present themselves. As Symington so clearly demonstrated, the relation of the height of the heart to the anterior chest-wall is the same as in the adult, but the diaphragm rises higher, and this contributes to the rounded appearance of the child's heart.

The size of the heart from birth to six years has been the subject of a formidable study by Bassochi,[10] who sought to establish an index by which, from the three cardiac dimensions observed radiologically in the living subject, the weight and volume of the myocardial mass could be calculated. He found that during this age-period the maximal measurements were in male children. He quotes Vannucci, who found that from birth to ten years the heart was larger in males, from ten to thirteen years larger in females, and above thirteen again larger in males. These figures show but slight discrepancy from those of E. M. Lincoln and R. Spillman,[11] who from studies of 246 normal children found that girls had smaller hearts than boys from two to seven years, and hearts the same size from seven to eleven years, while from twelve to thirteen the girls' hearts were still larger. They also found a closer correlation between heart-size and height than between heart-size and age. Hodges, Adams, and Gordon[12] have reduced the height, weight, and heart-size relationship to mathematical formulæ, and state that the heart area in square centimetres as shown in the "frontal plane silhouette" by X-ray, may be predicted in normal adults by the formula :—

$$F = 0.87H + 0.34W - 63.8$$

and in normal children by—

$$F = 0.180H + 1.045W + 13.7$$

(F = area in sq. cm.; H = height in cm.; W = weight in kilog.)

But M. G. Josephi[13] found this table accurate within ten per cent. in only fifty-three per cent. of children, and considers that there is closer correlation between cardiac surface-area and body surface-area, than between cardiac surface-area and height or weight. So those of us who are not very good at sums may enjoy a temporary respite, as the next formula is likely to be more complicated.

Hirch and Shapiro divided normal adult hearts into four groups : the short, broad heart of hypersthenic habitus, the long, thin heart of asthenic habitus, the true drop heart of hyposthenic habitus, and the common type of sthenic habitus. E. M. Lincoln and Spillman[11] found that children's hearts correspond closely with these types, the majority (166 of 246) falling into the common or "sthenic" type. They found, however, that prominence of the right border was not unusual, and that in twenty per cent. the outline of the pulmonary artery was accentuated, and in 1.3 per cent. markedly accentuated, without any evidence of pathological significance.

3.6 per cent. of the series had small hearts, and eleven cases of the 246 showed "growth" hypertrophy; this is enlargement without evidence of diseases which, they say, may be detected "in röntgenograms in children as young as five years of age, but the clinical picture of increased percussion to the left, displacement of the point of maximum impulse outside the mamillary line, and heaving apical impulse was not apparent in any child before nine years of age." None of these children showed electro-cardiographic evidence of left ventricular preponderance, and "no other definite diagnostic features save possibly the fact that the R-wave was notched or split a little more frequently in these children than in the rest of the group." I think that most of us will recollect having encountered such cases, and having been puzzled by them. Of equal interest is another group, recently described by Parkinson,[8] in which the hypertrophy is apparent rather than real; these are the cases with slight scoliosis giving rise to a sufficient degree of displacement to make the heart appear to be enlarged to the left on screening—"on rotating such a patient a few degrees to the right, the heart appears normally placed and not at all enlarged. In other words, this positional correction removes an illusion of disease."

These considerations serve to show, *first,* that experience is required in the assessment of the factors which are necessarily variable—age, sex, height, weight, shape of chest, and height of diaphragm; *secondly,* that screening of the patient is, in many respects, more valuable than a single radiogram, since one can examine the heart from various angles; and, *thirdly,* that radiograms are invaluable not only because one can study the films in greater detail, but because they afford a permanent and comparable record. It is, therefore, essential that a technique should be used which is as accurately standardized as possible, the most important points being the distance of the patient from the rays, the accurate focussing of the rays in midline and at a standard level, and the exposure time.

In the case of the child whose heart is known to be diseased, accurate determination of the size of the heart is important : *first,* the degree of hypertrophy may be less than the auscultatory findings would lead one to expect; this is more likely to be the case if the valvular lesion is recent, for hypertrophy of heart muscle, like that of any other muscle, takes time to develop. *Secondly,* and this is much more frequent in my experience, the X-ray screen may reveal a much larger heart than one had expected; this, therefore, suggests a much longer history than had been elicited; the truth of this is borne out by the tendency of recent observers to discredit acute dilatation as a cause of cardiac enlargement. *Thirdly,* one must always remember Sir Thomas Lewis's[14] dictum : "The muscle of a greatly enlarged heart is essentially unsound." *Fourthly,* the distribution of the enlargement may afford most valuable information. In children over ten years the commonest cause of enlargement of the left auricle is mitral stenosis; of the left ventricle the chief cause of enlargement is aortic regurgitation, but mitral regurgitation may also be a cause, and the congenital lesions, notably co-arctation of the aorta and patent ductus arteriosus, must be remembered. Enlargement of the right auricle is most marked in children with congenital patency of the foramen ovale, and is to be expected in late mitral stenosis, but its presence is not to be assumed in every case

where the right border of the heart-shadow presents a convex outline. Enlargement of the right ventricle is found in established mitral disease commonly in association with congestive heart failure; chronic emphysema in childhood is usually the result of severe asthma, and the "right heart" syndrome of middle age is not common. Many congenital defects involve the pulmonary orifice, and therefore cause right ventricular hypertrophy.

4. Heart Sounds.—It is generally accepted that the first cardiac sound is partly muscular and partly valvular in origin. To my ear, the first sound of normal child's heart is lighter in quality, as if the muscular "susurrus" were less deep in tone than in the adult's. The pump is a smaller one, and is working at higher rate and against lower resistance. The second sound may be accentuated: when this is audible over the aortic area it suggests nephritis, for, as has been said, essential hypertension is rare in childhood; accentuation of the pulmonary second sound is not to be regarded as definite evidence of mitral stenosis, for it may be heard in normal children. True reduplication or splitting of the second sound into its aortic and pulmonary components was described by Vaquez[15] as audible over the base of the heart in mitral stenosis; in early stenosis the reduplication was of "aortic precession"; at a later stage the valves were again synchronous; in the latest stage the pulmonary element was heard first—"pulmonary precession." In rare cases I have found this "aortic precession" to be distinguishable as a sign of commencing stenosis. At the apex of the heart the so-called reduplicated second sound is now known to be due to a third sound occurring at the opening of the mitral valve. Vaquez[15] emphasized the importance of this interpretation, and it is fully described by Bramwell,[16] who states that "it is probably produced by the valve cusps being set into vibration by the blood rushing under high pressure through the mitral and tricuspid orifices into the ventricles. When the blood can pass easily from auricle to ventricle no sound is produced; but when, owing to an increased rate of venous return to the heart, the velocity of the bood-flow is increased, or when the mitral orifice is constricted, as in mitral stenosis, a relative or actual obstruction is present. This favours the production of eddies in the ventricle, which set the flaps of the mitral valve into vibration, and so produce sound. In mitral stenosis, accentuation of the third sound is the usual finding." This third sound may be audible in health and much more frequently in youth than in persons of riper years. It may be so accentuated as to give rise to considerable difficulty in deciding whether it is the fore-runner of mitral stenosis. It is advisable to feel the pulse carefully for evidence of diminished volume, to examine the chest by X-ray for evidence of enlargement of the left auricle, and to see if the electro-cardiogram shows the large or notched P-wave of auricular over-action; but, as Sir T. Lewis says, "one sign only justifies the diagnosis (of mitral stenosis), and that is the appropriate murmur." This murmur is best heard in the recumbent position, or with the patient lying on his left side, and after moderate exercise. If there is no murmur at the apex, mitral stenosis is not to be diagnosed. If there is a mitral regurgitant murmur, the presence of an accentuated third sound is justifiably regarded as a herald of mitral stenosis. Probably the greatest difficulty in deciding

whether a child's heart is normal or not is when a murmur is present. "Functional" murmurs may occur over the pulmonary area, but are not infrequently heard at the apex; particularly in anæmic children, such murmurs are soft in quality, short and systolic in time, variable in intensity, are usually limited in area, have no definite line of conduction, and do not replace the first sound. Some authorities regard them as more often heard in the recumbent position, others as tending to disappear when the patient lies down. In the presence of any debilitating condition it may be difficult to exclude carditis, but repeated examination will soon settle the matter. It is better to enforce rest for a month than to insist on a child with early carditis going to school and playing games. If one must belong to one of Mr. Punch's[18] kinds of doctor, it is probably better to be a "wind-up" than a "pooh-pooh"!

5. HEART-RHYTHM AND THE ELECTRO-CARDIOGRAM.—The electro-cardiograph is of value for the differentiation of cardiac irregularity and of departures from the normal transmission of the wave of contraction throughout the heart muscle. By repeated cardiograms one may record the state of the heart at various stages in such illnesses as acute rheumatism or diphtheria, or note the effect of treatment. There is considerable individual variation in electro-cardiograms, and this does not simplify their interpretation. The T-wave tends to be deeper and broader in children, particularly in leads 1 and 2. T_3 was found by E. M. Lincoln and Gertrude Nicholson[20] to be inverted in 35.5 per cent. of 222 normal children.

Inversion of T_1 and T_2 is regarded as evidence of myocardial change, but may be temporary in character. The question of ventricular preponderance is not always easy. I have frequently found evidence of preponderance of one or other ventricle where I did not expect it on clinical grounds, and, more frequently, I have failed to find such evidence in cases where, clinically, I expected it; again, the presence or absence of preponderance of one or other ventricle has not always been confirmed by the radiologist's report on the X-ray findings. Right ventricular preponderance in older children is usually associated with mitral stenosis; if it is present in a child under ten years it strongly suggests a congenital lesion. Left ventricular preponderance is commonly found with aortic regurgitation. If mitral stenosis and aortic regurgitation occur in the same patient, left ventricular predominance is the common finding; there are, however, certain cases of combined aortic and mitral diseases where the electro-cardiogram has remained normal for a long period, suggesting that a certain balance has been achieved.

Heart-block of partial type, as evidenced by delay between the auricular and ventricular waves, is not very rare in acute carditis, but is very rare in the smouldering rheumatism of the out-patient. I have never seen the electro-cardiogram of a bundle-branch block in a child. Auricular fibrillation is rare in childhood; when present it is of very grave significance, not merely because of its mechanical handicap to the work of the heart, but because it only occurs when the heart is seriously diseased. Auricular flutter, with its rapid and regular pulse, is, in my experience, equally rare and of equally bad prognosis. More than fifty per cent. of normal children have SINUS ARRHYTHMIA. It may be regarded as evidence of the sensitivity of the nervous mechanism of the heart to impulses controlling respira-

tion. It tends to disappear in early life, but when it persists it may be regarded as evidence of health; on the other hand, its presence is no proof that a heart has escaped rheumatic carditis, as it is not infrequently detected in hearts which are obviously diseased. It is often more easily demonstrated clinically than by graphic methods, as the excitement of being electro-cardiographed increases the heart-rate and causes its temporary elimination. This is even more frequently noticed when EXTRA-SYSTOLES are present; a first electro-cardiogram may fail to demonstrate them, but repeated records, made when the patient "settles down," show the extra beats. Extra-systoles were not found in E. M. Lincoln and G. H. B. Nicholson's[20] series of electro-cardiographic examinations of 222 normal children. I have myself come to regard extra-systoles as of much more serious significance in children than in adults. They may be the first demonstrable evidence of carditis, as in a recent case, where they persisted for months before a mitral systolic murmur became audible. One instinctively looks for a focus of infection, but the removal of such foci as infected teeth and tonsils does not always give the reward which the patient deserves. This form of arrhythmia is not infrequent in children, and its presence should be regarded as evidence of organic disease until this can be definitely excluded.

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The Heart in Middle Age

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A recent monogram issued by the Metropolitan Life Insurance Company, New York, on "The Mortality from the Principal Cardio-vascular Renal Diseases During the Twenty-Years Period from 1911 till 1930," shows how great a factor these diseases are in influencing the death-rate. For the age period 1-24 years approximately eight per cent. of all deaths are due to cardio-vascular renal diseases, with the highest incidence at 10-14. Above 34 the incidence increases with each decade, and we find in the 35-44 years period a death-rate percentage of 19.8 per cent., 45-54 years of 32 per cent., 55-64 of 44 per cent., while from 65-74 years it reaches 55.3 per cent. of all deaths. This increase in the death incidence is easily understood when one considers the changes found in the circulatory system with advancing years, and the stresses, strains, chronic and other infections to which the human frame is subject.

The majority of cardiac deaths in children and young adults are due either to congenital heart-lesions or to the ravages of the rheumatic group of diseases on the valves, pericardium, and myocardium, and in many cases it is only because a relatively healthy myocardium is able to compensate for a serious defect, that life, restricted in many ways though it be, is prolonged for many years.

In considering the heart from middle age on, we have two main groups. First, that in which there is a previous lesion, such as an endocarditis or a pericarditis; and the second group, which becomes larger with each succeeding decade, a group including the high-pressure cases, the arterio-sclerotic, syphilitic, hyperthyroid, and those cardio-vascular lesions associated with other chronic or acute toxæmias.

Rheumatic Valvular Disease.

The introduction of auscultation, after Laennec invented the stethoscope in 1816, made the finding and differentiation of murmurs the one important clinical sign of cardio-vascular disease. The fact that a murmur was present, no matter how trifling the lesion, often meant a life of restrictions for the unfortunate patient, who frequently outlived the doctor responsible for the grave prognosis. This exaggerated idea of the importance of murmurs is gradually dying out, so that now one has to consider the type and degree of the murmur in conjunction with the alteration in the size and shape of the heart, more especially as regards the response of the heart to exercise. Of the cases examined in middle life, many have been diagnosed in childhood or young adult life, but in some cases, owing to the absence of symptoms and of a definite history of acute illness, the murmur may only be discovered during a routine examination. The prognosis in all cases depends ultimately on the heart-muscle. The greater the strain thrown on the muscle, the greater the risk of failure. Marked cases of mitral stenosis and aortic incompetence are the worst, while aortic stenosis and mitral regurgitation are less severe.

Mitral Disease.

In mitral regurgitation the whole heart as a rule hypertrophies, with a varying

degree of dilatation of the left ventricle and auricle. The size of the heart is important, as the larger the heart the greater the valvular defect, and if we exclude the activity of the valve-lesion, the greater the risk of failure. In mitral stenosis the left ventricle may be even smaller than normal, and the chief strain is on the left auricle and right ventricle. This leads to dilatation of the pulmonary vessels, and the greater the increase in the pulmonary shadow on X-ray examination, the worse the prognosis. Clinically we find a diastolic murmur, the Graham Steele murmur, which is always a grave prognostic sign and is associated with pulmonary circulation failure, as evidenced by engorgement of the veins of the arms and neck, congestion of the liver, cyanosis, and œdema. Auricular fibrillation is another complication of mitral disease, though in many cases it does not seem to make the prognosis much worse.

In aortic valvular disease, the left ventricle is affected in both stenosis and regurgitation, but it is only when the ventricle begins to fail, and a relative mitral regurgitation develops, that the other chambers are affected. The more marked the valve-lesion, the greater the hypertrophy, and, when failure occurs, the less likelihood of response to treatment. The degree of regurgitation can be estimated by taking the blood-pressure, as one generally finds that the more grave the lesion the lower the diastolic pressure and the higher the pulse pressure. The presence of a stenosis, by reducing the regurgitation, helps the prognosis. Another factor in regurgitation is the interference with the coronary circulation. Failure of the left ventricle leads to a failure in the peripheral circulation, and later to a failure in the pulmonary.

Apart from the actual valve-lesion, there are many other conditions which may be the determining factor in prognosis. Occupation is one of the most important. A patient who has to do heavy manual work cannot expect to compete in life expectancy with a clerk, and a clerk who leads too sedentary a life, and overeats with the common sequel of overweight, has a worse outlook than his fellow-clerk who takes adequate exercise and is not a gross feeder.

Infection, either focal or general, may be the main cause of the onset of cardiac failure. General infections, such as influenza, necessitate a more prolonged convalescence than in the average case. Focal infections, such as teeth, tonsils, cholecystitis, and other chronic infections, by interfering with the general health of the patient, react on the heart apart from direct changes in the myocardium. There seems to be an unjustified fear of removing such foci in case a subacute bacterial endocarditis develops.

In women, the risk of pregnancy has to be considered, but no hard and fast rule can be made in deciding which cardiac case is fit to bear children. Most cases of valvular diseases which are fully compensated and have not an active endocarditis can go to full term, and many have had several children. If a patient has had failure of compensation, or if the cardiac changes are severe, one should advise against pregnancy, and, if it occurs, early termination is generally necessary.

Dyspnœa, feeling of fatigue, and other symptoms in cases of valvular diseases, may be due to presence of anæmia, and diagnosis of the type of the anæmia with its appropriate treatment usually restores normal cardiac function.

Too much treatment may be, and often is, one of the reasons why a case of valvular disease does not regain greater health and greater cardiac response to effort. Cases are frequently admitted to hospital who immediately respond to the simple treatment of stopping digitalis, which has been gradually producing an accumulative toxic effect. The presence of a murmur in itself is not an indication that the patient should be digitalized.

Raised Blood-Pressure and Arterio-Sclerosis.

Essential hypertension or hyperiesis are terms applied to cases of hypertension without renal or other pathological changes. A pre-clinical stage has been described where the pressure is raised with normal stimuli, later returning to normal, but gradually progressing into a chronic hypertensive state. The causation of this condition seems to depend on many factors, most important of which is the hereditary tendency associated with nervous instability of the patient. Other factors are obesity and chronic infections. The condition tends to be progressive, and in many cases leads to renal and arterio-sclerotic changes with their symptoms and sequelæ.

The lay mind is too apt to develop a blood-pressure complex, a certain means of aggravating a by no means serious clinical state; and it is usually a grave mistake to tell a patient his pressure or to restrict his or her activities too much. Nervous relaxation is aimed at, and this is impossible if a patient's mind is continually filled with the dread of "blood-pressure." Treatment should aim chiefly at regulating a patient's life, his occupation, his home and social activities. Diet depends on the build of the patient, but, as most tend to adiposity, restriction of fats and carbohydrates rather than of protein is necessary. Septic foci should be removed, constipation treated by insisting on a regular habit-time, and by a mild purgative such as Kaylene-Ol, followed by a morning saline every other morning. Moderate exercise in the form of daily walks should be enforced. Alteration in the home and social surroundings is a more difficult problem, as few can leave a nagging wife or a dissipated husband for longer than the temporary holiday which a doctor usually orders. Emotional strain is a recognized factor in producing essential hypertension, and in women raised pressure is frequently found at the menopause, a time when emotional upset is common. Adequate rest in these cases is essential, not only physical rest, but a change from the worries and anxieties of home and children.

The hypertensive cases associated with renal, cardio-vascular, or thyroid changes are a much more serious problem. Arterio-sclerosis of the peripheral circulation may be marked without any rise in pressure, and many of these cases live to old age, with surprisingly few symptoms. It is when the coronary or renal vessels are involved that trouble may be expected. Cardiac changes are hypertrophy and enlargement, due to the pressure, and a gradually increasing interstitial myocarditis, due to deficient coronary circulation. This coronary defect may lead to the acute lesion of occlusion or to a more gradual myocardial failure, with the symptoms and signs of failing compensation, or we may have arrhythmias such as auricular fibrillation, extrasystoles, or heart-block. All these irregularities, as well as failure of compensation, must be looked on as more serious than when found in the

rheumatic group, on account of the coronary and interstitial myocardial changes, which make the heart less able to respond to treatment.

Various clinical signs in this group of cases may point to danger. Thus, gallop rhythm, only found when tachycardia is present, may be the first sign of approaching danger. In other cases, angina of effort, increasing dyspnœa or paroxysmal attacks of dyspnœa, or marked cardiac enlargement may be the danger signals. *Pulsus alternans,* best diagnosed when taking the blood-pressure, is always a serious sign. It is in this group that valuable help can be had from electro-cardiographic examination, as accurate diagnosis of irregularities, of myocardial changes, as evidenced by alterations in the T-wave and of coronary thrombosis, can usually be made from the cardiogram, and, with this proof of danger, adequate rest can be insisted on. Retinal changes are always of serious prognostic significance, and retinal hæmorrhages may be an early sign of danger in many cases. A high diastolic pressure is more serious than a high systolic. When there is marked cardiac enlargement, or there are signs of marked cerebral arterio-sclerosis, it is a mistake to try to lower the blood-pressure to any extent. One of the signs of a failing myocardium is a fall in pressure, and an improvement is usually followed by a rise in blood-pressure. Sudden falls in pressure lead to either serious myocardial failure, or to alarming cerebral symptoms.

Syphilis.

The cardio-vascular changes of syphilis are usually a late manifestation of this ubiquitous disease. The usual time factor is from ten to twenty or more years after the primary infection. The aorta and the myocardium are usually affected, though to varying degrees, and the condition can be suspected from the symptoms of fatigue, pain—retrosternal in character and often occurring at night, dyspnœa either on effort or the characteristic paroxysmal dyspnœa waking the patient at night, terrifying dreams, and alteration in the complexion, which is of a sallow "blay" colour. The special symptoms and signs of aneurysm are due to pressure on various organs, and the peculiar gander cough, hoarseness, inequality of the pupils, pulsation in the upper part of the chest, are all well known.

Treatment is directed to symptoms and to the specific infection. Adequate rest is essential if symptoms are present, and digitalis, morphia, and other cardiac drugs may be necessary as in other cardiac cases. It is usual to start anti-syphilitic treatment with a course of iodides and mercury, to be followed later by courses of arsenic and bismuth. Once active therapy is started it should be continued for a long time, as, if the patient neglects to report for further injections, there is a tendency for serious relapses to occur. Rest in bed usually relieves retrosternal pain, unless due to aneurysmal pressure, but in some cases diuretin gr. x t.i.d. has proved efficacious.

Thyroid and Heart Disease.

The cardiac changes in well-developed hyperthyroidism are as a rule easily diagnosed. Tachycardia is always present, and may be associated with auricular fibrillation or other irregularities, with palpitation, with systolic murmurs, often with raised blood-pressure, and in severe cases with more marked myocardial

changes. Our difficulties arise in cases where the thyroid etiology is less easily diagnosed and the hyperthyroidism is masked. There may be no exopthalmos, but usually the glossy, shiny appearance of the eyes is present. No goitre may be visible, and no adenoma palpable, and the patient consults a doctor on account of dyspnœa, palpitation, irregularity of the pulse, nervousness, loss of energy, and often some loss of weight and sweating. Usually the statement that the heart is affected is emphasized. The clinical signs often show an overacting heart with a slapping apex-beat and a diffuse pericardial impulse. The blood-pressure is often raised, especially at the first examination, and the fact that the patient may have been told about the pressure only exaggerates the cardiac complex. The clammy hands, the glossy eyes, and the fine tremor of the fingers, with the obvious nervousness of the patient, should turn to attention to the thyroid. Many cases have been treated with digitalis with no benefit, and the therapeutic test of rest, iodine, and bromide often confirms our diagnosis. Unfortunately, the estimation of the basal metabolic rate is rarely of any value in these cases. One could not expect to get any other result than a raised rate when one considers the type of patient.

The thyroid in every case of auricular fibrillation in a non-rheumatic heart should be carefully examined, to exclude the possibility of a toxic adenoma being present. If present, the only treatment likely to cure is removal of the adenoma after a period of medical treatment. Opinions now differ as regards the correct pre-surgical treatment in these cases. All are agreed that rest, both mental and physical, bromides, and often digitalis, are required; but though most authorities state that iodine is contra-indicated, in some cases it seems to be definitely beneficial.

The hypothyroid heart is also one that presents difficulties in diagnosis. The stout, wheezy, elderly person is often doomed to a life of semi-invalidism with repeated courses of tonics, digitalis, and other drugs, when thyroid would work wonders. The fact that many cases have a high blood-pressure, some of over 200, and others show well-marked cardio-vascular changes, may mask the thyroid deficiency. Thus a patient seen in 1931, with a pressure of 180/110, enlarged heart, and definite electro-cardiographic changes, with symptoms of dyspnœa, precordial pain, and general lassitude, has been leading an active social life since she started to take thyroid regularly. In the myxœdematous patient the estimation of the basal metabolic rate is helpful, as a low reading confirms the clinical diagnosis, and the actual reading is a help in deciding the amount of thyroid required. If it is not feasible to have this test carried out, the therapeutic test of small doses of thyroid is of the greatest value.

In conclusion, the main thing to remember is, that these cardiac cases in middle age require to have their mode of living regulated, rather than to be considered invalids. The presence of a murmur, or of a raised pressure, should not be emphasized too strongly, unless the patient has symptoms such as those of failing compensation, or of pain. Dyspnœa may be due to anæmia, adiposity, or hypothyroidism; while pain, though apparently anginal in character, may be secondary to some abdominal lesion, or to some toxic process such as septic foci, excessive tobacco, or other over-indulgence, and treatment of these often prevents more serious myocardial or coronary changes.

Heart Disease Complicating Pregnancy

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THIS article is a commentary on sixty-nine cases of heart-disease in pregnancy, compiled from data obtained by personal observation. Most of the cases were treated in the Belfast and Royal Maternity Hospitals.

The lesion in every case was mitral stenosis. In eighteen cases mitral regurgitation was also present, and inefficiency of the aortic valve was superimposed in five.

Forty-six patients, of 66.6 per cent., had suffered from at least one attack of acute rheumatic fever; five, or 7.35 per cent., had had scarlet fever, and a similar number gave a history of frequent sore throats. Three patients, 4.3 per cent., had suffered from chorea in childhood, and in ten cases, or 14.4 per cent., a history of previous illness could not be elicited.

All these cases run concurrently; the cardiac lesion was in no case discovered accidentally on routine examination. Each patient came seeking advice for symptoms pointing to failure of cardiac efficiency.

The first symptom in the train of cardiac failure in pregnancy is breathlessness, and patients complained of it in ninety-eight per cent. of cases. It probably is the result of several factors, e.g., failure of the myocardium, and increased oxygen requirements. However, on closely questioning forty-five patients in a previous series,[1] thirty stated definitely that the onset of breathlessness coincided with the time life was first felt. The explanation probably is that, at the time of quickening (eighteenth to twentieth week), the uterus, which then reaches almost to the umbilicus, is of such a size that the movements of the diaphragm are impaired. As as result, there is a decrease in vital capacity. In the normal patient, breathlessness is not noticed, but in the patient with some diminution in the cardiac reserve, this symptom appears, and is undoubtedly the earliest symptom of a breakdown in compensation.

Occurring almost as frequently, there is an increase in the pulse-rate, and this is the earliest sign of myocardial failure in these cases. The following table shows the average pulse-rate, for the first three days, in patients admitted to hospital:—

In 36 cases the pulse-rate was over 120								
,, 16	,,		,,	,,	between 110 and 120			
,, 7	,,		,,	,,	,,	100	,,	110
,, 6	,,		,,	,,	,,	90	,,	100
,, 4	,,		,,	,,	,,	80	,,	90

The diseased heart in pregnancy has additional calls made upon its reserve: thus it has to cater for (1) the actual lesion, (2) increased blood-volume and oxygen requirements, (3) increased abdominal tension with consequent embarrassment of the diaphragm, (4) increase of body-weight, (5) possible toxæmic states causing rise in blood-pressure, (6) marked increase in muscular effort during labour. These all throw an increased strain upon the heart, and it is not surprising, therefore, that few women with a diseased heart will go through pregnancy and labour.

particularly pregnancy, without showing some effects of inroad on their myocardial reserve.

Seventy per cent. of the cases were quite well when they were not pregnant, save for some dyspnœa on violent exertion, e.g., running upstairs, but every case was suffering from failing compensation when first examined. Forty-six patients (sixty-six per cent.) required rest in bed with digitalis before the thirtieth week of pregnancy, and sixteen (twenty-three per cent.) were delivered by Cæsarean section.

Prognosis.—To the statement that in most pregnant women with heart-disease some failure of cardiac reserve occurs, the natural sequence is a discussion on the prognosis in such cases. Without a proper conception of prognosis, treatment of these cases cannot be properly carried out.

It is generally agreed that lesions at the mitral valve have the worst prognosis. The actual lesion, however, is in itself of little value in assessing the outlook in any given case. Rather, the main points to be noted are the extent of the failure of compensation, and the reaction to adequate treatment. It must be remembered, too, that the extra strain imposed on the heart is progressive and cumulative, culminating in a vigorous muscular effort. In addition, rheumatic lesions are prone to be progressive, so that there may also be increased damage to the heart, and consequent impairment of compensation from this cause. In this connection, therefore, it is of importance in considering prognosis to know the period of time since the last attack of acute rheumatic manifestation. Where the heart is well compensated at the outset of pregnancy, the patient may continue, even through labour, fairly well, although there is always some depletion of cardiac reserve. On the other hand, if there is any failure of compensation at the outset, then pregnancy and parturition will become dangerous.

The degree of impairment of cardiac reserve is assessed on the signs and symptoms of failing compensation, signs being of more value than symptoms. In this connection, Sir James Mackenzie[2] lays greatest stress on the capacity of the heart for increased effort. Pregnancy and labour are one great effort. A fairly accurate conception of the response to effort may be obtained if the signs and symptoms in a case treated for decompensation are compared during the period of rest, and again when the patient is pursuing routine duties. In a case where compensation is well established, there will be little or no alteration in the pulse- and respiration-rates taken during rest, and immediately after mild exercise, e.g., walking round the room for a short time.

The New York Heart Association has drawn up standards, grading cases with a view to prognosis and treatment. The groups are as follows :—

Group 1—Patients without symptoms, i.e., well-compensated cases.

Group 2*a*—Patients with slight limitation of activity.

Group 2*b*—Patients with definite limitation of activity.

Group 3—Patients whose cardiac reserve is at a minimum.

Gilchrist[3] states that Group 1 patients do well, and come through pregnancy and labour with very little damage to the heart; patients of Group 2*a* usually present no difficulty; those of 2*b* manage pregnancy and labour when they have had adequate ante-natal treatment. Patients in Group 3 rarely survive.

In a series of ninety-five cases which he grouped in this classification, thirteen fell into Group 1, all of whom delivered themselves normally, and there were no deaths. There were twenty-six patients in Group 2*a*; twenty were delivered normally, two were treated by Cæsarean section, and there were no deaths. Forty-five patients were graded into Group 2*b*. After rest in bed, 55.6 per cent. were delivered normally. Where rest and digitalis were required, Cæsarean section was performed (28.8 per cent.). There were two deaths in this group. In Group 3 there were eleven cases; 9 per cent. were delivered normally, 54.6 per cent. by Cæsarean section, and six patients (over 50 per cent.), died.

Leyland Robinson,[4] in a report on eighteen cases of heart-disease in pregnancy, complicated by auricular fibrillation, and where compensation was at a minimum, gives a death-rate of thirteen, i.e., seventy-two per cent.

In the series under review there were three deaths, a mortality-rate of 4.3 per cent. Statistics on mortality in pregnancy complicated by heart-disease vary from two to eighty per cent., but De Lee[5] states that a fair average is 6.3 per cent. Fitzgibbon,[6] reviewing a series of twenty-two cases, had five deaths, while Stander[13] with eighty-one cases had a mortality-rate of 1.37 per cent. The first fatal case in my series occurred in a primipara on the eighteenth day of the puerperium after a spontaneous labour, lasting thirty hours, at the thirty-fourth week. The second was sudden collapse in a six-para, forty-eight hours after a spontaneous full-term labour of one and a half hours. The third death occurred four hours after Cæsarean section in a primipara, with a marked degree of decompensation, and who had had no ante-natal treatment.

While there is no doubt of the deleterious effect of pregnancy on the diseased heart, yet the following table of the cases under review shows that fifty-one patients had borne 207 children. The cardiac lesion must have been present in some, if not all, of the pregnancies, and since rheumatic affections are commonest in childhood, it is probable that in many cases the heart was injured before the first pregnancy. Each pregnancy undoubtedly causes further depletion of reserve, but it can be seen from the table that the prognosis in cardiac cases in pregnancy is not too grave.

Number of patients	*Per cent.*	*Number of times pregnant*
18	26.09	1
9	11.60	2
12	17.39	3
7	10.14	4
5	7.25	5
6	8.69	6
2	2.89	7
3	4.33	8
4	5.79	9
2	2.89	10
1	1.47	11
1	1.47	12

TREATMENT.—Factors influencing the treatment of heart-disease in pregnancy are (1) degree of compensation, (2) parity, (3) response to treatment, (4) age, (5) interval since onset of causal condition, (6) relative values of induction of premature labour and Cæsarean section, (7) number, maturity, and nature of previous confinements, (8) maturity, (9) interval since last pregnancy, (10) presence of obstetrical complications.

The main consideration in all cases is the degree of compensation, and all other factors must always be of secondary importance.

The following is a record of the sixty-nine cases in this series :—

Induction of miscarriage	5
Normal delivery at term	36
Normal delivery, following induction, at or near thirty-six weeks	4
Forceps deliveries at term	2
Abdominal hysterotomy and sterilization before twenty-eight weeks	3
Cæsarean section and sterilization at or near term	16

Three cases did not return to hospital after treatment for failing compensation.

In all cases a close watch must be kept for signs of decrease in the reserve power of the heart, and treatment instituted at the first appearance of such signs. Forty-six (sixty-six per cent.) of the cases under review required rest in bed with digitalis before the thirtieth week of pregnancy, on account of failing compensation. Such patients must be kept in bed on absolute rest, and digitalis, as the tincture or granules, given in the usual doses till compensation is re-established and the pulse slow and steady. Davis[7] lays stress on the restriction of fluids in the diet, and goes so far as to advocate the use of purgatives, e.g., Epsom salts, to obtain fluid abstraction from the bowel. Where stimulation of the heart is required, he advises strophanthin, and strychnine where there is a fall in blood-pressure. In the cases in my series, where compensation was restored after treatment, four weeks was the average length of stay in bed before their condition was considered satisfactory. As soon as compensation is restored in such cases, termination of the pregnancy is advised by Newman.[8]

In patients where there is any degree of cardiac inefficiency in the early months, termination of the pregnancy must be considered. If the cardiac reserve is so much depleted that symptoms are present in the early months, any attempt to carry on the pregnancy will not only be of no avail, but definitely dangerous. Such cases should have the pregnancy terminated as soon as the cardiac condition can be raised to its highest possible degree of efficiency. There were eight such cases in the series under discussion, five of whom were treated by balloon induction and curettage after miscarriage, and in three abdominal hysterotomy with sterilization was performed.

Patients in whom the heart begins to fail in the later months should be treated by

rest in bed and digitalis therapy, on the lines indicated above. If compensation is restored, they should be carefully watched against a further breakdown, but if this does not occur, normal labour, as in my series, generally follows. Termination of pregnancy is imperative if these cases fail to improve or if any improvement is only temporary. The ideal line of treatment then is Cæsarean section and sterilization, and is undoubtedly the treatment of election in cases where compensation cannot be recovered, or where it breaks down again after treatment. Sixteen of the cases in my series were treated by this method. This may seem a high percentage—twenty-three per cent., but six of these cases were multiparæ, and a factor in deciding upon Cæsarean section was that it afforded at the same time an ideal method of treatment with opportunity for sterilization.

There is no doubt that in many cases where Cæsarean section or abdominal hysterotomy is required, sterilization should at the same time be performed. If the patient's condition warrants either of these operations, it certainly demands sterilization. The same view is held by Hamilton and Kellog[9] of Boston, who regard the indications for termination of pregnancy as indications for sterilization.

Induction of labour has no place in the treatment of the failing heart in the later months. It may require several anæsthetics, and labour may be prolonged over several days. Nervous and physical strain may become considerable, and often there is a fair amount of bleeding. When the condition of a patient in the last few weeks is so grave that termination of pregnancy is necessary, it is at the same time far too serious to allow the risks of repeated anæsthetics, protracted labour, and manipulative measures, so often the accompaniment of induction. By the time the induction of labour is successful, the patient is not in a fit state for further anæsthetics or operative procedures.

With regard to the termination of pregnancy in the earlier months, several methods are available—induction by balloons, vaginal hysterotomy, and abdominal hysterotomy. Of these, abdominal hysterotomy is the best : it holds the same high place in the early months as does Cæsarean section in the later months.

Up to fourteen or sixteen weeks maturity, I have found an easy method to be the insertion of two or three sea-tangle tents into the cervix and through the internal os, without an anæsthetic. The patients do not object to this in the slightest. It requires only a few minutes to insert the tents, and there is no pain accompanying or following the procedure.

In forty-eight hours, under anæsthesia, the tents are removed. One finger can now be inserted into the uterine cavity, and the uterus evacuated rapidly and safely.

Pardee[11] is of the opinion that in the earlier months induction by the vagina does not seriously disturb the circulation.

Cæsarean section and abdominal hysterotomy are reasonably safe, can be performed rapidly, and each allows of sterilization without increasing the risks of the operation.

On the other hand, however, some authorities, among whom are Reis and Frankenthal,[10] are of the opinion that no attempt should be made to sterilize the

patient at Cæsarean section, preferring to wait for a few months till the cardiac condition has improved, and then performing this operation.

Induction of miscarriage or premature labour in the presence of cardiac failure is to be strongly condemned. The additional strain of miscarriage or labour in a patient with failing compensation will almost certainly cause death, generally as a sudden collapse after delivery.

Lennie,[12] in an excellent paper, states that the results obtained from induction of labour by bougies are disastrous, and from induction of abortion and accouchement forcé are bad. For treatment by these methods he found the death-rate to be forty-four per cent.

Anæsthesia.—Most writers agree that gas and oxygen anæsthesia is the best in all operative procedure on cardiac patients. Newman, however, advocates open ether anæsthesia for forceps deliveries, while Gilchrist is in favour of chloroform and oxygen, or spinal anæsthesia.

Labour.—Spontaneous labour in cardiac cases, as a rule, does not give rise to anxiety, for it is generally quick and easy : the wind is tempered to the shorn lamb. On examining the labour records of the cases in this series, I found the average duration of labour to be just under seven hours. These cases included two patients on whom induction of labour was performed and where labour was prolonged over thirty hours. This figure was made up regardless of the parity of the patients.

Reviewing a series of 102 cases of pregnancy complicated by heart-disease, Reis and Frankenthal[10] found the average duration of labour in primiparæ to be twelve hours, and in multiparæ seven and a half hours.

Various explanations have been given for this quickening of labour—for example, unusual softening of the cervix uteri due to pelvic engorgement, but it is probable that the most important factor in causing increased strength and frequency of the uterine contractions is the excess of CO_2 in the blood.

Since labour is generally rapid and easy, sedatives are not often required. For the same reason, delivery with forceps, although frequently advocated as soon as the os is fully dilated, is seldom necessary; but of forty-two cases in my series, delivered at or near term, forceps were used in only two, a rate of 4.7 per cent. One important advantage of delivery by forceps, however, is that it tends to minimize the risk of sudden cardiac failure from intense congestion during the final expulsive efforts of the second stage.

No patient collapsed during or immediately following the third stage, and in no case did port-partum hæmorrhage occur.

To guard against sudden collapse from too sudden evacuation of the uterus, an excellent safeguard is that advocated by the famous Smellie for the condition we now term obstetric shock. Smellie's nephew and successor, Dr. John Harvie, said in 1762 : "A warm double cloth must be laid on ye belly and *bound tight* to prevent too great quantity of blood from rushing into ye relaxed vessels of ye abdominal viscera, whereby ye head is robbed of its due proportion and dangerous faintings ensue."

I am indebted to Professor Miles H. Phillips of Sheffield for this quotation from a great British master of obstetrics, surely as good teaching to-day as it was then.

PUERPERIUM.—With the exception of one fatal case, in no patient did any cause for worry arise during the puerperium. Cardiac cases should be kept in bed longer than normal cases in order to give the myocardium time to make up its depleted reserves.

SUMMARY.—A series of sixty-nine cases of heart-disease in pregnancy is reviewed. In all cases extra strain is thrown upon the heart by pregnancy. Prognosis and treatment are to be considered in the light of the cardiac response to this strain.

In cases of cardiac failure in the early months of pregnancy, termination is advised, and is best performed by abdominal hysterotomy.

For failure of compensation, or return of failure after treatment, in the later months, Cæsarean section is the treatment of election.

Induction of miscarriage or of premature labour should never be performed in the presence of cardiac failure.

Labour, as a rule, is short and easy.

I have to thank Professor C. G. Lowry and Mr. H. L. H. Greer for permission to use the charts from which this article has been prepared.

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A Review of the Asthma Problem

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Definition of allergy. — The Greek word *allon* means 'different,' and the term 'allergy' was coined by Von Pirquet in 1911 to denote the state of "different" susceptibility to various substances that are harmless to the majority of normal persons. Von Pirquet intended the term to cover all forms of altered reaction, whether exaggerated or diminished : but, during the last twenty-five years, allergy has come to mean 'hyper-sensitiveness.' When doing the Von Pirquet test I often found that cases of advanced pulmonary tuberculosis gave no reaction to tuberculin. The term 'anergy' has been suggested for this diminution of sensitivity; but it does not appear to have come into general use.

The allergic group of diseases comprises asthma and hay-fever as respiratory manifestations; and migraine, mucous-colitis, and eczema as nervous, abdominal, and cutaneous examples respectively. It is stated that in this group a family history of allergy may occur in seventy-five per cent. of the cases.

The combination of asthma and hay-fever is common; and I have recently had a case who suffered from migraine in girlhood, then from eczema, and later from mucous-colitis. At present, at the age of 55, she is suffering from asthma.

The tendency to spasm is well marked in this group of diseases : for example, there is, in asthma, spasm of the bronchi; in mucous-colitis, spasm of the colon; and in migraine, probably spasm of one of the cerebral arteries.

It is difficult to discover what are the factors which determine that the allergic reaction will take the form of asthma. Heredity is of great importance, as also is lung trauma—previous injury to the lungs by such an illness as broncho-pneumonia. Nerve stimulation, either of the reflex area in the nose, or of the bronchioles by chronic bronchitis, may play a secondary part.

In attempting to review the problem of asthma, attention must be paid to the anatomy and physiology of the area concerned.

ANATOMY AND PHYSIOLOGY.

The respiratory bronchiole is the most important structure in asthma, because it is in this region that the seat of reaction lies. The muscle coat of the bronchiole forms a minute sphincter at the origin of the alveolus.

The thorax is essentially an inspiratory apparatus, and, even though the sphincter is constricted, air can still be sucked into the alveoli during inspiration, but it cannot escape so readily during expiration.

This alveolar distension gives rise to the feeling of "tightness" in the chest and to "air-hunger." The patient gasps for air, so increasing the distension.

The sphincter also regulates the tension of the alveolar air. During closure of the sphincter the gaseous exchange is lessened, and a condition of gross *functional* emphysema exists. It is, of course, mechanical and temporary, whereas true emphysema is structural and continuous. It is obvious that the great difficulty will be

deflation. The most successful treatment is that which deflates. This explains the success of adrenalin. It also explains the reason why respiratory exercises have been introduced in the treatment of asthma.

During constriction of the bronchioles, the ducts of their glands will be obstructed and secretion will be scanty. Relaxation of the spasm by adrenalin will set free the choked-up secretion, so it is usually abundant at the end of the attack.

The forcing of the secretion through the duct orifices and the tiny bronchioles results in the formation of the threads known as "Curschmann's spirals." It is futile to give iodide of potassium to "loosen the sputum." It is not a question of loosening the sputum, but of loosening the spasm.

In the long axis of the bronchus, the muscle constitutes a sort of myo-elastic layer. This takes a spiral form, a branching tubular network, like the parallels of latitude and longitude strung round a globe. These myo-elastic fibres, running from the hilum along the bronchial tree, may go as far towards the periphery as the respiratory epithelium and form the minute sphincters.

These myo-elastic spirals are hauled in towards the hilum during expiration, like a fisherman hauling in his net. It is this gentle myo-elastic recoil on the hilum that deflates the alveoli. If the muscle is in spasm, in asthma, lung recoil and deflation must be seriously affected. The presence of the cartilaginous rings in the bronchioles prevents complete occlusion of the air-tube, and consequent atelectasis. I have never seen atelectasis occur in asthma.

Another factor preventing atelectasis is fatigue. It is impossible that all the bronchioles should be constricted at once. During an attack of asthma, sibilant rhonchi are heard; but if any given part of the chest is continuously observed, the sibili appear and disappear. One gets the impression that, though the majority of the bronchioles are in contraction, "yet at all times an appreciable number of these tubes are relaxed, as if resting, before springing again into the spasm, while their neighbours earn a brief respite." The left auricle is closely attached to the lung-root by the pulmonary veins. Therefore, diastole of the left auricle is more aided by lung recoil than by any other factor. If lung recoil is interfered with, as in asthma or emphysema, auricular filling will suffer. Long-standing venous congestion in the lungs will probably result in the onset of fibrillation, since the auricular muscle is relatively weak.

Venous engorgement means an overburdened auricle, and an overburdened auricle means cardiac defeat.

Bronchospasm is the protective reflex normally found when irritating fumes or vapours are inhaled. It is possible that, in asthma, the same protective reflex is employed to shut off the entry of dust containing allergens to which the patient is sensitive.

The presence of bronchospasm can be shown when an attempt is made to introduce lipiodol into the bronchi in some of these asthmatic patients. The spasm is so complete that the lipiodol is not found except in the larger bronchi on the X-ray film.

A more difficult problem is the presence of spasm of the intercostal muscles and of the diaphragm.

During an attack of asthma, the diaphragm can be seen, on screening, to be depressed to its fullest extent. Only spasmodic attempts at movement are being made. In the long run, this will result in actual shortening of the muscle-fibres of the diaphragm. Deformities of the thorax, such as Harrison's sulcus, may occur as a result of this.

It is difficult to understand why spasm of the diaphragm should occur, as the phrenic nerve does not seem to be involved in asthma.

The contraction of the accessory muscles of respiration, and of the intercostals, which occurs in asthma, may also result in chest deformity. "The muscles tend to adopt a new postural length and tone."

The Allergens.

The list of substances which may provoke an allergic reaction presents an extraordinary diversity.

Bray classifies them under five headings:—Inhalants, ingestants, infectants, injectants, and contactants.

There are several points of interest in the group of inhalants. Patients who suffer from hay-fever may also suffer from asthma. I have seen several cases of this type. At the Asthma Clinic at St. Mary's Hospital, it is claimed that every case of hay-fever has been cured, and that densensitization is accompanied by loss of skin sensitivity, and of the sensitizing power of the serum. It is obvious that this offers much opportunity for research.

It has further been suggested that "house asthma" is due to the presence of moulds or fungi in old houses. The Asthma Research Council are investigating the sputum of patients attending their clinics for the presence of monilia. In those showing infection, the cutaneous reactions to monilia are being tested.

It has often been noticed that asthmatics show marked improvement under treatment in the wards of the Royal Victoria Hospital. This may be due to "passive avoidance" of the allergen. The air is warmed, and filtered through screens of wet roping, hence it is freed from the dust and smoke of a great city. The wards are modern, floors and walls being polished, and corners rounded to avoid accumulation of dust. The psychological factor of "expectation" may also assist in the treatment. Recently the Asthma Research Council have been attempting to densensitize patients with solutions of feathers, hairs, and dust, buffered with adrenalin to prevent undue reactions.

Inhalant sensitivity is being recognized as more important than sensitivity to food or to bacteria.

I have seen a case of asthma where the allergen was a vegetable dusting-powder used to protect cattle from warble-fly.

It is a well-known fact that asthma may be produced by various ingestants. These need not necessarily be protein. Aspirin is an example of a non-protein ingestant.

The question of infectants will be discussed under the section dealing with

"Lung Trauma." Injectants such as therapeutic sera, and contactants such as silk, form a relatively small percentage of recognized allergens.

This extraordinary diversity of allergens leaves one faced with the fact that the patient may become sensitive to almost anything. So it is obvious that not much information can be gained from study of the allergens.

In allergic conditions, a local reaction is found at the site of the "allergic outburst," and this local reaction takes the form of eosinophilia. This localized eosinophilia is a local response to protein irritant, and examples are the presence of eosinophils in the bronchioles and the sputum in asthma, and in the cutaneous reactions in urticaria.

The slight increase of eosinophils in the blood-count is held to be a secondary condition.

An interesting example of the presence of a foreign protein in the serum is given by the Prausnitz-Küstner reaction.

The serum of Küstner, who was sensitive to fish protein, was introduced into the skin of Prausnitz. It was then found, on ingestion of fish-protein by Prausnitz, that his skin had become locally and passively sensitized to fish-protein, with the formation of a wheal at the sensitized site. This is known as "passive transfer," or as "reaction by proxy."

Much controversy has taken place over the presence of a proteose in the urine (Oriel's proteose) in cases of asthma. The statement is made that the blood can digest peptone. If proteose, an allied substance, is excreted in the urine, it suggests deficient power on the part of the blood to destroy peptones.

These reactions are held to be proof of the presence of an unknown protein in the blood. In asthma "union of this antigen with an antibody releases an unknown substance which acts on the vagus centre and produces the asthmatic explosion."

Some observers hold that this unknown substance is either histamine or a substance (termed by Lewis the "H-substance") which has a similar action.

When histamine is injected intravenously into animals it causes shock, with smooth muscle contraction, as in the bronchi; and when applied to the skin it leads to the formation of wheals, akin to the cutaneous manifestations found in an allergic subject.

After this brief review of allergic phenomena, the question of the "make-up" or diathesis of the asthmatic patient must be considered, and a separate section will be allotted to this subject.

The "Asthmatic Diathesis."

In considering the asthmatic diathesis, the following factors must be taken into consideration :

a. The psychic factor.
b. Lung trauma.
c. The endocrine factor.
d. Hypochlorhydria.
e. The nasal factor.

The Psychic Factor.—The question of heredity in asthma is too vast a subject to be entered upon in a short review of this type. Diagrams are given in the text-books showing, for example, fifteen allergic patients in a family group of eighteen persons. It is probably a Mendelian phenomenon.

Given this allergic diathesis, an attack of asthma can be produced reflexly by emotion as by any of the allergens already considered. It has been said that "psychic trauma is merely the trigger which fires the allergic gun."

The asthmatic patient is often of superior intelligence, and burdened with heavy business or professional responsibilities. Dread of an attack must constantly be present, and must lead to the formation of an anxiety-neurosis.

Others describe asthma as a "conditioned reflex"—the term made familiar by the experiments of Pavlov. Mental associations are said to be formed between certain objects or places and asthmatic paroxysms. A well-known example is the asthmatic, sensitive to roses, in whom an attack was induced by the sight of an artificial rose. Similarly, patients who have had attacks in certain places, may have further attacks when these places are revisited. This may be due to auto-suggestion in patients with an allergic diathesis. "Week-end asthma" may, perhaps, be included in this group.

Witts and Conybeare have published a paper recording the results of treatment with normal saline solution. "The frequency of spontaneous recovery in these cases provides a factor which may be used in assessing the results of more specific treatment." Improvement under treatment with normal saline must be a further example of auto-suggestion.

The fact, however, that most attacks of asthma occur during sleep is a useful corrective to those who are inclined to emphasize unduly the psychic factor.

Lung Trauma.—This type may occur in childhood, after the age of five years, but it occurs more frequently in adults. There is a history in children of whooping-cough, or measles, followed by bronchitis or broncho-pneumonia.

In adults I have seen cases follow broncho-pneumonia, pneumonia, and "gassing" due to war service.

The X-ray chest generally shows a large amount of lung trauma, chiefly in the form of dense fibrosis radiating from the hilum. There is often a pure culture in the sputum of an organism such as pneumococcus or streptococcus. This produces a coincident bronchitis.

The asthma may be due to irritation of the bronchioles from the bronchitis, or to sensitization by bacterial allergens.

I believe this type of case to be commoner than is generally supposed. Broncho-pneumonia in children often leaves a residue of unresolved basal patches, which may lead to fibrosis or even bronchiectasis. Permanent improvement is not to be looked for, owing to the structural change in the lung, but symptomatic improvement is sometimes obtained by vaccines.

Though the distension of the alveoli in asthma is transitory and mechanical, and in emphysema is permanent and structural, yet it is obvious that long-continued asthma may lead to true emphysema.

Hurst points out that if sufficient freedom from attacks is given, the distended alveoli in asthma tend to return to normal. This is not possible in true emphysema, where the distension is pathological, with atrophy and rupture of the alveolar walls.

Owing to the defect in venous emptying into the left auricle, venous engorgement will occur in the long run. Sooner or later the signs of a cardiac defeat will be manifested. When this occurs in the emphysematous asthmatic, venesection gives very good results.

I have seen one case of bronchitis and asthma in a child where subcutaneous emphysema resulted after a paroxysm of coughing. Rupture of a distended, adherent, emphysematous bleb was followed by escape of air into the subcutaneous tissues, chiefly round the neck and face, but also over thorax and abdomen. Death occurred in this case probably from infection of the subcutaneous tissues.

Now the commonest lung trauma in Northern Ireland is pulmonary tuberculosis, and it is remarkable how rarely the two diseases occur together. Various workers (Burger, Bray, and others) record the opinion that there appears to be a real antagonism between these two diseases.

Some confusion appears to have arisen from the fact that Van Leeuwen, in 1925, advocated treatment of asthmatics by tuberculin. He proposed to use this in a non-specific way, using the proteins of tuberculin as those of peptone are used.

It is now held that the response of a tuberculous patient to tuberculin is an example of allergy. Therefore, if asthma were tuberculous in origin, or if the two diseases co-existed, one would expect allergic reactions. When working in Ward 8 of the Royal Victoria Hospital, with the late Professor MacIlwaine, we tried the effect of tuberculin on many cases of asthma, but we were unable to elicit any reactions.

The Endocrine Factor.—Since adrenalin relieves bronchial spasm, it is tempting to ascribe asthma to adrenal deficiency. But asthma does not occur in Addison's disease.

The allergic patient is stated to have a blood-sugar lower than the average. The clinical use of glucose, especially in children, has been advocated for years. It may owe its efficacy to increasing the store of liver glycogen.

There exists a small group of cases where the symptoms of hyperthyroidism, or toxic goitre, and asthma are present at the same time. These are known as endocrine asthma.

Widal has described a small group of four cases, and an American observer has described three cases. Now, in toxic goitre the following symptoms are due to sympathetic stimulation :—(*a*) Exophthalmos, (*b*) dilated pupils, (*c*) retracted eyelids. This gives the patient the pecular bright, brilliant gaze. The swarthy, earthy tint of the skin found in advanced cases may be due to adrenal involvement, also of sympathetic origin.

The nerve supply to the thyroid is from the middle sympathetic ganglion. In these cases of sympathetic stimulation, the bronchi must obviously be dilated. In asthma they are contracted. How, then, can asthma and toxic goitre co-exist?

I have seen one case of this type in Ward 1 of the Royal Victoria Hospital,

Belfast, in September, 1935. The symptoms of exophthalmic goitre were well marked. The basal metabolic rate was +32. The patient also had well-marked nocturnal asthma. She was very sensitive to adrenalin. It relieved the asthmatic spasm, but it also produced—

1. Increased tachycardia.
2. A sense of præcordial distress.
3. Marked tremor.
4. Noises in the head "like the ringing of a bell."
5. Transient glycosuria.

The effect was curiously delayed, and an injection given about 2 p.m. produced its maximum effect at 10 p.m.

Endocrine asthma is not affected by climatic change or by diet, and skin-tests are uniformly negative. It is aggravated by emotional shock and menstruation. All the usual medication employed in asthma is useless.

Some protrusion of the eyeballs, with tachycardia, and swelling of the neck may accompany the dyspnœa of asthma, and may be overlooked. An asthmatic may show wasting, sallow, pigmented skin, and psycho-neurotic changes.

"One might suppose," says Widal, "that it is by an instability of the vegetative nervous system, provoked by endocrine dysfunction, that thyroid disease can produce asthma. It is not possible to analyze the process of this instability, so curious that it can occur in patients with endocrine lesions, which renders patients susceptible to react to phenomena of shock to slight influences."

The American observer records *retrosternal* goitre as a possible cause of asthma, but probably the dyspnœa, due to pressure on the trachea, would be more in the nature of stridor than asthma. X-ray or clinical observation did not disclose retrosternal goitre in the Royal Victoria Hospital case.

Treatment should be directed to the thyroid if the asthma is to be improved.

The Royal Victoria Hospital patient had nine exposures to deep X-ray therapy. She stated that she had gained a stone in weight, that her asthma was much improved, and that she felt more comfortable.

Partial thyroidectomy has also been recommended.

Hypochlorhydria. — In normal persons, hypochlorhydria is more common in middle age. In asthma it is more common in childhood, and in these cases the curve of age incidence of hypochlorhydria runs parallel with that of the age incidence of asthma, the highest point of each curve being in childhood.

Low free acidity was found in fifty-one per cent. of one series of cases of asthma; in forty-one per cent. the total acid was also low.

There is also excess of mucus in the fasting juice, and the low free acid value may be partly due to this excess mucus.

It must be also remembered that excess mucus is partly due to chronic gastritis which accompanies long ill-health. It may also be due to inhibition of the gastric secretion by the administration of cod-liver oil and fatty foods to delicate asthmatic children.

An interesting speculation is that the substance producing the allergic reaction is not destroyed by the digestion when hydrochloric acid is absent. In this manner

foreign protein may gain access to the blood. It is claimed that great improvement is produced by the administration of hydrochloric acid.

The Nasal Factor.—Physicians are now inclined to regard the nasal factor as of secondary importance only. Nasal abnormalities are held to be secondary to nasal allergic manifestations, thickening and hyperplasia of the nasal mucosa being produced by the repeated swelling of the mucosa caused by œdema. Modern treatment should be, as far as possible, non-surgical and conservative.

Status Asthmaticus.

In this condition severe asthma continues almost without interruption for days. Death may recur from cardiac failure, anoxæmia, or long-standing pulmonary congestion. In the last case of this type I saw, the doctor made the acute observation that œdema of the lungs had probably set in, as the patient was bringing up large quantities of clear, frothy, blood-stained sputum. Treatment in this case was successful, and it was on these lines :—

1. The "continuous adrenalin" method advocated by Hurst. Three minims of adrenalin were given hypodermically every half-hour.
2. Continuous oxygen administration by the nasal catheter.
3. Cardiac stimulants hypodermically : caffein, coramine, strychnine.
4. Plenty of fluids by the mouth, including glucose and alcohol.

Treatment.

Respiratory Exercises.—One of the most striking advances in treatment of late has been the attempt to lessen movement of the affected lung by measures directed to control movement of the chest-wall. To this group belong all the varieties of collapse-therapy now used in the treatment of tuberculosis, such as artificial pneumothorax, phrenic avulsion, and thoracoplasty.

Respiratory exercises are being introduced as an attempt to control deflation of the alveoli via the chest-wall.

It has been shown that the chronic asthmatic, even in the periods between his attacks, has learned a wrong use of his muscles of respiration. Because of his dyspnœa, he tries to breathe deeply, and so over-distends the lungs, which are already over-inflated.

The danger is that his chest, owing to shortening of the accessory muscles of respiration, will become fixed in the "inspiratory" position. How can this be avoided? One group of exercises is of the "blowing-out type." Inhalation is short and expiration prolonged. These exercises aim at "emptying" the lung.

A second group of exercises is used to make the diaphragm do as much of the work as possible, and a third group aims at "increasing the flexibility of the chest-wall."

If the exercises prove beneficial there should be an increase in chest measurement, and in diaphragmatic excursion, and the time occupied in expiration should be lengthened.

Bacterial Vaccines.—These are obviously of most use in cases of the "lung trauma" group, where there is definite infection of the respiratory tract, and where there are one or two organisms only present in the sputum.

The initial doses should be small, and it has been suggested that they should be given intradermally instead of subcutaneously, to avoid undue reaction. Asthmatic patients are often very sensitive to bacterial vaccines, and a course of treatment may be prolonged owing to the necessity of keeping the dosage small.

In my experience, densensitization by bacterial vaccines is often successful, and the patient remains free from attacks.

In some cases, however, the results are indefinite, especially in those cases where the X-ray shows very marked fibrous changes in the lungs. This method appears, at least, to be a logical and scientific attempt to solve the difficult problem of desensitization.

Desensitization by Non-specific Proteins.—The use of tuberculin in this connection has been mentioned in the section on lung trauma. Personally, I have not seen good results or lasting improvement follow its use. Van Leeuwen in his "Allergic Diseases" claims that fifty per cent. of his asthmatic cases treated by tuberculin had no further attacks.

Other substances which have been used in the attempt to densensitize by non-specific methods are milk, peptone, and sulphur, but the results so far appear to be very disappointing.

The Asthma Research Council record that at one of their centres non-specific desensitization is being attempted by liver extract (campolon), in doses of from 0.5 c.c. weekly. Results of treatment by this method will be awaited with interest.

Asthma Powders and Sprays.—These are only mentioned in order that their use may be condemned. The danger is that the patient may become a drug addict, as many of these preparations are said to contain cocaine. This point is well illustrated by a case recently reported at length in the medical journals, in which a patient attempted to recover damages from his doctor on the ground that the spray prescribed had led to his becoming a cocaine addict.

Methods to Relieve Spasm.—Adrenalin and ephedrin are so well known that they need scarcely be considered in detail. Tremor and tachycardia, induced by their use, are a result of sympathetic stimulation.

I have no experience of the use of benzyl-benzoate as an antispasmodic in asthma.

Miscellaneous.—Potassium is liberated in the serum of animals on stimulation of the sympathetic. It has been tried in treatment, but without avail. A similar remark applies to acetyl-choline, a product of vagus stimulation.

The use of aspirin in asthma has been recommended, but a small proportion of patients are aspirin-sensitive.

Theoretically atropin should be a drug of value in relaxing vagal spasm, and it sometimes gives good results.

In this short review I have tried to show how complex and many-sided is the problem of asthma, considered as one of the allergic group of diseases. The allergic reaction may perhaps be best summed up in the words of Robert Bridges, Poet Laureate and Doctor of Medicine:

> "By a secret miracle of chemistry
> We hold internal poise upon a razor edge
> That may not even be blunted, lest we sicken and die."

The Treatment of Furunculosis and Other Staphylococcal Lesions by Staphylococcal Toxoid

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THE discovery that many strains of staphylococci produce a toxin (Neisser and Wechsberg, 1901[1]; Kraus and Pibream, 1906[2]; Parker, 1924[3]; and Burnet, 1929[4]) has thrown fresh light on the problem of the treatment of staphylococcal lesions.

From staphylococcal toxin, Panton, Valentine, and Dix (1931)[5] successfully prepared staphylococcal toxoid.

In 1933 Parish[6] found that staphylococcal toxoid was innocuous to laboratory animals and was an efficient immunizing agent, causing an increase in the circulating antibody. Parish, O'Meara, and Clarke[7] published the results of further investigations in 1934. They found that the sera of numerous laboratory animals and human subjects contained appreciable amounts of natural anti-toxin.

Staphylococcal toxoid was first used clinically in the treatment of staphylococcal lesions by Panton and Valentine (1932)[8], and by Dolman (1933).[9] The results they obtained were sufficiently encouraging to induce other workers to investigate its effect in the treatment of various lesions due to the staphylococcus. Among these were Connor[10] in Australia, Dolman[9] in Canada, and K. S. Murray[11] in England. Their results, based on the treatment of a large number of cases, made it evident that in staphylococcal toxoid, a rational and reasonably successful method has been made available for the treatment of the chronic and resistant infections due to this organism.

The series of observations on which this article is based was begun in December, 1934, and since then ninety-eight cases have been treated.

CLINICAL RESULTS OF TREATMENT.

The cases have been classified into four groups according to the clinical result obtained. These groups are :—"Recovered," "Markedly Improved," "Improved," and "Unaltered."

Those classified as recovered were the patients whose lesions completely disappeared during the course of treatment. They were not regarded as cured until their condition had remained perfectly satisfactory for at least six months after the conclusion of treatment.

TABLE I.

SUMMARY OF RESULTS.

Result	*Number of cases*	*Percentage*
Recovered - - -	21	30.8
Markedly improved - -	25	36.7
Improved - - -	16	23.5
Unaltered - - -	6	8.8

On consideration of these results, it is evident that ninety-one per cent. of the cases treated derived benefit from the treatment, and that in thirty per cent. of all cases the treatment proved completely successful.

Many of the cases classified as "Markedly improved" have been so grouped because, although their lesions have quite disappeared, their treatment only ceased within the last six months. In six cases, or 8.8 per cent., the treatment was a complete failure. In a few cases relapses occurred some time after the conclusion of their treatment, but on receiving a second course of injections, the lesions again cleared up, and since then the patients have remained well.

A few cases had recrudescences during the course of treatment, but eventually their condition showed a definite if slight improvement. Apart from the disappearance of the local lesion, patients often experience an increased sense of well-being during treatment. Fifteen of them volunteered the information that their appetites had improved; they felt more energetic and better in general health since beginning the course of injections. The beneficial effect on the health of the children treated was especially noteworthy.

TABLE II.

RESULTS IN MORE DETAIL.

Lesion	*Recovered*	*Improved*	*Unaltered*	*Total*
Acne Keloid -	—	1	1	2
Acne with Staph. -	—	11	1	12
Boils - -	17	11	1	29
Dermatitis - -	1	2	—	3
Meibomian Cysts -	—	2	—	2
Styes - -	5	1	—	6
Sycosis Barbæ -	2	3	2	7

On consideration of the results obtained in various clinical conditions, we find that most success is attained in cases of recurrent furunculosis. Twenty-nine cases of boils were treated; seventeen of these made a complete recovery, eight showed marked improvement, and three showed only slight improvement. The boils usually disappear after two or three injections, and do not recur. Some cases improve more slowly; the lesions as they occur become more and more superficial and heal faster, until they finally cease to appear. It has been noted that in these cases fresh lesions may appear two to three days after the weekly injection, especially during the first two or three weeks, although there may be no other evidence of reaction.

The results obtained in acne with staphylococcal infection have proved disappointing. Of twelve cases, none could be described as cured, though all except one showed improvement. The percentage of relapses was high.

Seven cases of sycosis barbæ are included in this series. Two of them remained unaltered by the treatment, but the others were definitely improved, two of them having remained free from trouble for several months.

Good results have been obtained in the treatment of styes. Of six cases treated,

five became completely free from lesions and the sixth improved to a slight degree. Some of these cases were of long standing.

A few cases of blepharitis were treated with satisfactory results, and two cases of meibomian cysts yielded to treatment after a prolonged course of injections. Both these patients need a small course of two or three injections at intervals of a few months in order to keep their lids in a normal condition. In one of them the condition had been present for five years before treatment by toxoid was begun.

Dolman (1935)[12] states that he obtained good results in patients with staphylococcal infections of the nose and nasal sinuses. Three cases in the present series had such an infection, two of them combining the nasal infection with pustules and dermatitis around the nose and upper lip. These two patients did very well, making a complete recovery after a prolonged course of treatment. The third had only a few injections, without any change in his nasal discharge or chronic pharyngitis.

In two cases of furunculosis a certain degree of improvement took place during the course of treatment, but although treatment was continued they made no further progress. When, however, treatment was stopped, they made a quick recovery. This effect has also been noted by Murray (1935),[11] and he suggests as an explanation that the staphylococcus has produced a degree of toxæmia which it takes some time for the circulating anti-toxin to overcome.

Since infection with the staphylococcus is almost universal, it is not unlikely that a great deal of minor ill-health should be due to the toxic effects of its products. That this is probable is shown by the marked improvement in general health which often occurs during a course of injections of staphylococcal toxoid.

Method of Treatment.

The preparation of staphylococcal toxoid used was that supplied by Burroughs, Welcome & Co. It is supplied in two strengths, one ten times stronger than the other. Patients were generally given a course of six to eight injections, beginning with a dose of 0.1 or 0.2 c.c. of the dilute toxoid. The injections were given intramuscularly, at weekly intervals, and the doses were increased progressively according to whether reactions followed their administration or not. Murray[11] and Dolman[9] both recommend an initial dose of 0.5 c.c. of dilute toxoid. This we have found to be too strong an initial dose, as in several of our cases it gave rise to a marked general disturbance. We find that very small doses give rise to no other disturbance than a slight soreness at the seat of injection.

The course of injections given in most cases was 0.2, 0.5, and 0.75 c.c. of the dilute toxoid, followed by 0.1, 0.2, and 0.4 of the strong toxoid. In some cases this plan could not be followed because of the marked general reactions which occurred in these patients even when small doses were given. Consequently treatment by the small doses tolerated had to be continued over a longer period, up to nineteen doses having been given in a few instances. This prolonged method of treatment was also adopted in those patients whose lesions were slow in improving. In both types of case the results obtained were satisfactory.

The dosage depends upon the individual patient and his reaction to toxoid. One has to be guided by the individual and his response just as in giving vaccines. For example, one patient could tolerate a dose of only 0.3 c.c. of dilute toxoid, but as the result of fifteen injections he made a complete recovery from a long-standing furunculosis.

Reactions.

Notes of reactions were made in forty-three cases. Of these, sixteen, or thirty-nine per cent., observed no reaction whatever. The usual type of reaction which occurred was a slight soreness and stiffness at the site of injection; this can be disregarded from the point of view of increase of dosage. It was accompanied in twenty-five per cent. of cases by a mild general reaction, the patients complaining of headache and malaise which occurred during the evening following the injection.

The more severe type of local reaction was characterized by tenderness, swelling, and redness at the site of injection. The needle puncture was surrounded by an area of redness sometimes up to three inches or more in diameter. This appeared twelve hours after the inoculation, and lasted two or three days. Often it was accompanied by headache.

Severe general reactions occurred in seven cases, or sixteen per cent. of the patients treated. There was very marked malaise with severe headache, general aching, restlessness, and sleeplessness. These symptoms came on some hours after the injections, and sometimes continued into the following day, although they became less severe as time went on. There was probably a rise in temperature, although temperatures were not recorded.

Nausea and giddiness occurred in a few cases, and one or two patients complained of a feeling of nausea which lasted for some days.

In two patients the first injection (of 0.5 c.c. dilute toxoid) had rather a curious effect. Three hours after the injection of toxoid their vision became blurred and they were unable to see print or even large objects clearly. The condition passed off in half an hour, and was followed by headache. A third patient had similar symptoms, but in a lesser degree, and in his case it was accompanied by itching of both eyes. This man had a much smaller initial dose than the other two.

If the initial dose is small, and care is taken not to increase the dose too rapidly, reactions give rise to very little trouble.

Several children have been treated in our series, and in none of them did any reactions occur, thus confirming Dolman's statement (1935)[12] that in children the inoculations give rise to very little discomfort.

Dolman (1935)[12] also states that the tolerance which adults develop to later doses is soon lost, and if a lapse of one month has occurred since the last dose of toxoid, the initial dose of any supplementary course should not be more than 0.1 c.c. of the strong toxoid. Our results confirm this finding, and in addition we have found that during the course of prolonged treatment it is sometimes necessary to reduce the dose, as the patient may begin to show reactions to a larger dose if it is continued over a number of weeks.

In six cases an exacerbation of the local lesion followed the first one or two injections.

Effect of the Inoculation of Staphylococcal Toxoid upon the Circulating Anti-toxin.

The total number of cases treated and followed up was sixty-eight. In almost all cases the amount of circulating anti-toxin in the blood was estimated before treatment. Estimations were carried out on ninety-five sera taken from patients before treatment was begun, and the average amount of anti-toxin present in these sera was found to be one international unit. The method used for this estimation was that devised by Parish, O'Meara, and Clarke[7] in 1934. It consists in the titration of the amount of anti-toxin present in a serum, the result being expressed in terms of international units. (Parish—personal communication.)

Table III.

Units of Circulating Anti-toxin in the Blood Before and After Treatment.

Number of cases treated	*Units before treatment*	*Units after treatment with six to eight doses of toxoid (0.62 c.c.)*
68	1	7.7

The result shown in the above table is in accordance with Murray's observation that four doses of toxoid increase the initial value of the circulating anti-toxin almost eightfold. The figures given are the averages calculated from these sixty-eight cases.

Table IV.

Units of Circulating Anti-toxin in the Blood Before and After Treatment in Different Clinical Conditions.

Cases	*Average initial titre*	*Average titre after six to eight weeks treatment*	*Average amount toxoid given*
Acne Keloid -	1	5	0.96 c.c.
Acne with Staph.	0.75	8	0.45 c.c.
Boils - -	1	5	0.79 c.c.
Dermatitis -	2	10	0.57 c.c.
Meibomian Cysts -	1	5	1.55 c.c.
Styes - -	0.4	8	0.57 c.c.
Sycosis Barbæ -	2	8	0.5 c.c.

From this table it may be deduced that the increase of circulating anti-toxin is not affected by the type or situation of the staphylococcal infection. Also, the increase in the circulating anti-toxin bears no relationship to the amount of toxoid given.

As regards the production of anti-toxin, it was also noted that two main types of response could be distinguished. Some patients acquire anti-toxin very slowly,

reach a comparatively low titre (three units), and lose their acquired anti-toxin equally slowly. On the other hand, some respond quickly, reach a high titre in a short time (up to thirty-eight units has been noted), and lose their acquired anti-toxin almost as quickly as they produce it.

Clinically, the members of the first group seem to have somewhat better results than those of the second group, but the numbers are not large enough to allow of definite conclusions being drawn.

TABLE V.

RESULTS SHOWING THE AVERAGE INCREASE OF ANTI-TOXIN IN EACH GROUP.

Result	*Units before treatment*	*Units after treatment*
Recovered - - -	0.75	9.3
Markedly improved - -	1.5	8
Slightly improved - -	0.75	11
Unaltered - -	0.4	5

On the whole, there is no relationship between the anti-toxin produced and the clinical result, as is shown in Table V.

The effect of the prolonged injection of toxoid was noted in twenty-three cases. Frequent estimations of the anti-toxic content of the blood of these patients were carried out. In nine of them a continuous increase of circulating anti-toxin was produced, but in the remaining fourteen there was either no change or an actual fall in the anti-toxic content of the blood. The average fall observed was from eleven units to three units. It was found that the anti-toxic titre of the blood always falls when treatment is stopped, but it seldom or never reaches its original level, and, indeed, seldom goes below two or three units in amount.

In those cases liable to recurrences, the estimation of the anti-toxic content of the blood is useful, because it enables us to determine if and when a further course of treatment is advisable. It also serves as a guide in the treatment of those cases which need a small dose every two or three weeks to keep them free from lesions.

VACCINE TREATMENT.

Almost all the patients who came for treatment with staphylococcal toxoid had had previous courses of vaccines, either stock or autogenous. In most of these cases vaccine treatment was quite without results; in a few it was responsible for a temporary recovery, but was without effect on being tried a second time.

A possible explanation of the occasional success of vaccine therapy may be found in the observation made by Burnet (1930),[13] and confirmed by Parish, O'Meara, and Clarke,[7] that the toxins produced by different strains of staphylococcus aureus vary in potency. If, therefore, the strain of staphylococcus aureus used to make the vaccine is a highly toxigenic one, that may account for its success when used in vaccine therapy.

With regard to the effect of vaccine therapy on the amount of circulating anti-toxin in the blood, it was found that the average amount present in the bloods of

all those who had had vaccines was 0.89 units, while the average amount present in the bloods of those who had been treated with autogenous vaccines was two units.

Inoculation by staphylococcal toxoid marks a distinct advance in the treatment of staphylococcal lesions, but much further work remains to be done in the investigation of other products of the staphylococcus. Evidence is accumulating to show that there is more than one toxin produced by the staphylococcus, and also that this organism produces other substances which are concerned in infection and immunity. The polyvalency of the staphylococcal toxins may account for some of the failures in treatment which are at present inexplicable.

Summary.

1. The inoculation of staphylococcal toxoid produces an increase in the antitoxin circulating in the blood.

2. In ninety per cent. of the cases treated, definite improvement of their clinical condition resulted.

3. Six per cent. of cases showed no response.

4. Reactions following inoculations are not troublesome if the plan of giving an initial dose of 0.1 or 0.2 c.c. of dilute toxoid is adhered to.

5. The general health of patients often shows marked improvement.

6. Children respond well, and reactions are not troublesome in their cases. The same dosage was given no matter what the age of the patient.

7. Patients suffering from furunculosis, dermatitis, and styes are most likely to have a favourable result.

I have much pleasure in acknowledging the willing help and co-operation of Dr. McCaw, Dr. Lewis, and Dr. N. C. Graham in the carrying out of this work.

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A Case of Agranulocytosis

By J. T. Lewis, B.SC., M.D., F.R.C.P.LOND.

Royal Victoria Hospital, Belfast

THE clinical features of agranulocytosis, and the frequent development of the condition following the administration of pyramidon, are now widely recognized. The following case is sufficiently typical to be worth recording :—

Mrs. E. W., aged 53. Seen with Dr. J. Unsworth on 2nd April, 1936. There was a history of about one week's illness with a "septic throat," pyrexia, vomiting, and occasional rigors. The patient looked ill, with slight cyanosis, and some respiratory distress. Temperature 101° F., and pulse 130.

There was extensive ulceration of the fauces, with a greyish slough on both tonsils. The cervical glands were not markedly enlarged, and the liver and spleen were not palpable.

There was nothing else noteworthy on physical examination except profound prostration. A swab from the tonsils had been reported negative for bac. diphtheriæ.

The general features of the case suggested the possibility of agranulocytosis, and on inquiry it was found that the patient had been taking a preparation which probably contained pyramidon. It was not possible to find out how much of this had been taken.

Investigations.—Leucocytes, 2,800 per cmm. No polymorphonuclear cells seen in two films, leucocytes were entirely lymphocytes, mainly of the large type.

Blood-culture : sterile. Throat-swab : many spirochætes and fusiform bacilli present, with hæmolytic streptococci. No diphtheria bacilli detected. (The presence of large numbers of Vincent's organisms in the throat is not uncommon in agranulocytosis.)

Nucleotide therapy was advised, and during the next four days the patient received 80 c.c. pentose nucleotide by intramuscular injection, in divided doses. There was no evidence of clinical improvement.

On 6th April she was admitted to the Royal Victoria Hospital. The temperature was then 102° F., pulse 136, respirations 56. Blood-count : Hb = sixty-two per cent. ; red cells = 3,280,000 per cmm. ; white cells = 800 per cmm. Film showed no polymorphonuclear leucocytes, platelets normal. She received a further 25 c.c. nucleotide solution.

On 7th April her condition was worse, and she had developed definite signs of broncho-pneumonia. The blood-film showed only an occasional lymphocyte. She died on the same afternoon.

In this case there was no evidence of bone-marrow response after five days of moderately intensive nucleotide therapy.

Liver extract was not used, although it is considered by Witts and others to be of service in agranulocytosis.

Post-Mortem Note.

A post-mortem examination was carried out some eighteen hours after death. The only gross pathological changes were a firm greyish consolidation of the upper lobe of the right lung, a red consolidation of the lower lobe of the left lung, ulceration of the Peyer's patches and of the solitary follicles of the ileum, and fatty changes in the liver. The marrow of the upper third of the right femur was fatty and showed no leucoblastic reaction.

Microscopically, the marrow of the upper third of the right femur exhibits a predominance of myeloblasts with a smaller proportion of myelocytes. No mature granulocytes can be seen. Megakerocytes are not reduced in number. The liver is the seat of fatty changes, and is free from cellular infiltration of any kind. On the other hand, the kidney exhibits numerous foci of cellular infiltration in the boundary zone, and many of the cells conform in their general histological characters to myeloblasts. The ulceration of the small intestine is attended by a mononuclear infiltration of the submucous and muscular coats, and bears a notable resemblance to typhoid ulceration. The consolidation of the lungs is peculiar in the respect that the air-sacs are turgid with a homogenous exudate. This exudate has been shown to contain a large proportion of fibrin by Gram's stain, but polymorphonuclear leucocytes are entirely absent.

ULSTER MEDICAL SOCIETY.

The annual golf competition was held at the Royal County Down Golf Club, Newcastle, by kind permission of the captain and council. The president (Dr. Foster Coates) entertained the Fellows and Members to lunch and tea. The competition, which was eighteen holes against bogey, resulted in a tie between Dr. F. Barnes Elwood and Dr. H. Hilton Stewart, each being "all square." The replay resulted in a win for Dr. Stewart at the seventeenth hole.

Fellows and Members will be pleased to learn that, owing to the generosity of the president, a handsome panel containing the names of all the presidents of the Society has been erected in the hall of the Whitla Medical Institute.

BRITISH MEDICAL ASSOCIATION, ANNUAL MEETING, 1937

By the time this report is in print the Arrangements Committee in London will have settled a provisional programme for the Belfast Meeting in July. May we take this opportunity of reminding local members that only when we have some idea of the funds at our disposal will it be possible to make any detailed plans for the entertainment of our guests. If this is to be on the same scale as at previous meetings, we should aim at raising locally about £2,000. Only about £1,000 has been subscribed up to date, so if you have not yet sent in your subscription, please let us have it as

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soon as possible. A good response now will save the funds money which would otherwise have to be spent on the printing and posting of circular letters. Subscriptions should be sent to the Honorary Treasurer, Mr. W. M. Fullerton, at the Head Office of the Ulster Bank Ltd.

S. T. IRWIN,
Chairman, Finance Committee.
R. W. M. STRAIN,
Hon. Local General Assistant Secretary.

BRITISH MEDICAL ASSOCIATION
TYRONE DIVISION

THE annual meeting was held in the Tyrone County Hospital on the 12th March, 1936, at 4.30 p.m.

The financial report for the year 1934-5 was presented by the secretary, approved of, and signed by the chairman.

The following was the result of the election of office-bearers :—Chairman, Dr. J. Chambers; vice-chairman, Dr. R. J. Spence; hon. secretary, Dr. J. R. Martin; hon. treasurer, Dr. G. A. M. Gillespie; representative on Branch Council, Dr. W. Lyle; representative on Representative Body, Dr. W. Lyle.

A special meeting was held in the Tyrone County Hospital on the 21st May, 1936, at 4.30 p.m.

The National Insurance Defence Trust was discussed, and the hon. secretary was instructed to write to the secretary of the Branch and find out the views of other Divisions, and notify the member of our Division on hearing from him.

As to the British Medical Association meeting in Belfast in July, 1937, the members were very enthusiastic about this, and many subscriptions were promised. The hon. secretary was instructed to draft out a circular and send it to all practitioners in County Tyrone, appealing for subscriptions.

As to a proposed amalgamation of the Tyrone and Fermanagh Divisions, on hearing from the latter, it was decided to drop the matter for the present.

A special meeting was held in the Tyrone County Hospital on 20th August, 1936, at 4.30 p.m., to discuss the scale of fees to dispensary medical officers in the immunization scheme against diphtheria. After full discussion, it was unanimously decided that a scale of seven shillings and sixpence per head, as laid down by the British Medical Association, be the minimum fee acceptable to the Tyrone Division. The hon. secretary of the Northern Ireland Branch was informed accordingly.

JOHN R. MARTIN, *Hon. Secretary.*

Holmdene, Clogher, Co. Tyrone.

REVIEWS

MANUAL OF EMERGENCIES: MEDICAL, SURGICAL, AND OBSTETRIC. THEIR PATHOLOGY, DIAGNOSIS, AND TREATMENT. By J. Snowman, M.D., M.R.C.P.Lond. Third Edition, 1936. John Bale, Sons & Danielsson, Ltd. Pp. 401.

The author of this little book attempts to cover a very wide field, and it may be said at once that he does so in a concise yet lucid manner. This is the third edition of the book, which shows that the author's efforts are appreciated. It has been completely revised and much of it has been rewritten, in order that the text should be thoroughly up to date. The emergencies caused by disease or accident to the various systems are first considered. Then follows a section on poisons, including protein poisons and food poisoning, which should prove of considerable value. The last section of the book is devoted to the dangerous emergencies in midwifery, hæmorrhage being especially fully dealt with.

This book is essentially one for the busy general practitioner, as it is handy for carrying around and yet contains detailed information on the treatment of the various emergencies with which he has to deal. The book is on the whole an excellent one, and this third edition should have as great a popularity and as extensive a circulation as the preceding editions.

LABORATORY PRACTICE. By J. R. Currie and Contributors. Edinburgh: E. & S. Livingstone, 1936. Pp. 378, figs. 169. Price 21s. net.

Professor Currie, in the introduction to this book, states that it is addressed primarily to medical graduates and licentiates, and therefore he assumes in the reader a knowledge of the scientific fundamentals which every qualified practitioner should have acquired during his medical training. Without such an assumption, it would have been impossible to convey in a work of its relatively modest dimensions any substantial instruction in all the variety of topics treated.

It is intended for use as a laboratory companion rather than for systematic study, yet, in spite of this limited field, it is easy to read, and in addition conveys a vast amount of theoretical information, particularly from the point of view of the value to public health of the various pieces of laboratory work described. For example, in the case of a food-test, relevant standards of food purity are noted, and in the case of a metazoon, its life history is described, so suggesting those stages against which repressive measures may most effectively be directed.

Professor Currie himself is responsible for most of this work, including the sections on chemistry, bacteriology, and meteorology. But the section on entomology was written expressly for this book by Dr. Robert A. Staig, and the section on helminthology by Miss Margaret W. Jepps, both of whom are Lecturers in Zoology in the University of Glasgow; while the section on protozoology was written by Dr. A. G. Mearns, Lecturer in Public Health in the same university.

The book is a remarkably good one, and in spite of the modest description given it by Professor Currie in his introduction, it is one that should be in the library of every Department of Public Health.

REVIEWS

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LABORATORY PRACTICE. By J. R. Currie and Contributors. Edinburgh: E. & S. Livingstone, 1936. Pp. 378, figs. 169. Price 21s. net.

Professor Currie, in the introduction to this book, states that it is addressed primarily to medical graduates and licentiates, and therefore he assumes in the reader a knowledge of the scientific fundamentals which every qualified practitioner should have acquired during his medical training. Without such an assumption, it would have been impossible to convey in a work of its relatively modest dimensions any substantial instruction in all the variety of topics treated.

It is intended for use as a laboratory companion rather than for systematic study, yet, in spite of this limited field, it is easy to read, and in addition conveys a vast amount of theoretical information, particularly from the point of view of the value to public health of the various pieces of laboratory work described. For example, in the case of a food-test, relevant standards of food purity are noted, and in the case of a metazoon, its life history is described, so suggesting those stages against which repressive measures may most effectively be directed.

Professor Currie himself is responsible for most of this work, including the sections on chemistry, bacteriology, and meteorology. But the section on entomology was written expressly for this book by Dr. Robert A. Staig, and the section on helminthology by Miss Margaret W. Jepps, both of whom are Lecturers in Zoology in the University of Glasgow; while the section on protozoology was written by Dr. A. G. Mearns, Lecturer in Public Health in the same university.

The book is a remarkably good one, and in spite of the modest description given it by Professor Currie in his introduction, it is one that should be in the library of every Department of Public Health.