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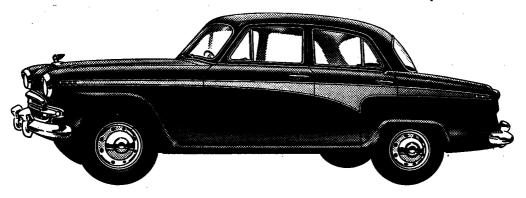
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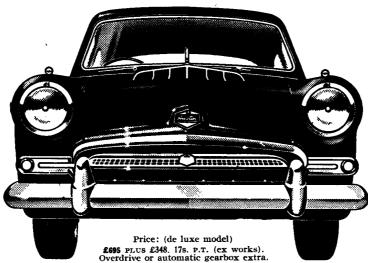
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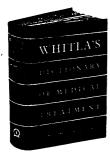


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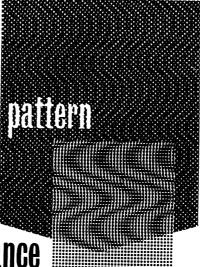
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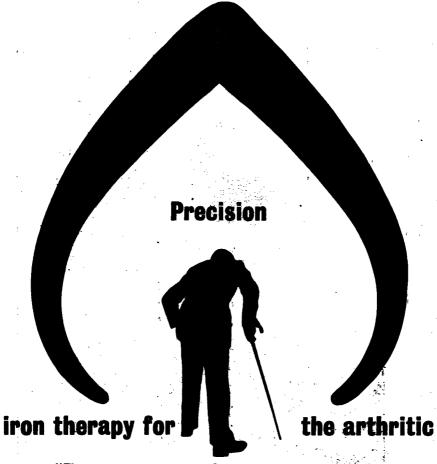


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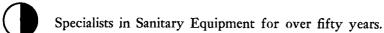
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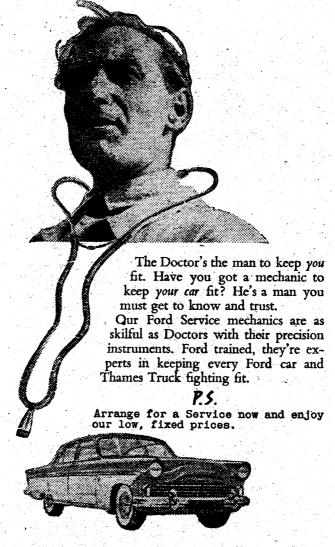
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### THE ULSTER MEDICAL JOURNAL

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### The Responsibility of the Surgeon to the Aged Patient

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### Presidential Address to the Ulster Medical Society, 31st January, 1957

THE Ulster Medical Society was formed in 1866 to further medical knowledge. It must not be lost sight of that dissemination of new knowledge and thought must be universal and then accepted before it can be considered a true advance. The work of the laboratory must pass beyond its limits to be clinically tested in the hospital wards and finally approved in general practice before it is considered a true advance in medicine. It is here in this Society that the laboratory worker, the consultant, and general practitioner mingle, discuss, and determine an advance. As President succeeds President, there is the thought that in that interval some new problem is being investigated and some advance recorded. It seemed to me fitting then that I might address you on a subject in which there has been a little advance and in which further problems are being confronted, and one which must become more important to surgeons in the future, namely, the surgeon's responsibility in the treatment of the older age groups. Each branch of medicine is dependent upon the other; as one section develops it throws upon the other the responsibility to make a commensurate advance. Old age is the result of advances in all branches of medicine, including hygiene and social medicine, so that surgeons must seek to play their part.

In Northern Ireland, with an estimated total population in 1964 of 1,432,900 total inhabitants, there will be:—

Females over 60 - - - 116,000
Males over 65 - - - 75,000
191,000

Hitherto the benefits of surgery have often with complacency been denied to the aged, thinking that the patient had already had a long life and the risk of operation so great that it was not justified. But the span of any life cannot be accurately estimated, and even a few months of life may be valuable. It it could be foreseen that one of us was to die in two years' time from an accident it would not justify a surgeon refusing to-day to sew up in us a perforated ulcer or remove an acute appendix. Old age has its rights as well as youth. Too old at 40 is a misnomer—66 per cent. of worthwhile world accomplishments have been done by people over 60. Saint Patrick was over 60 years when he came to Ireland on his mission of Christianity, and Franz Hals was over 80 before he thrust immortality upon the syndics of the almshouses of Haarlem, and it was after 80 years of age that Rembrandt portrayed most poignantly on canvas the joys and sorrows of the human soul. In our own age we have only to think of statesmen like Adenauer and Winston Churchill. These might say:—

"Grow old along with me!

The best is yet to be,

The last of life, for which the first was made."

Undoubtedly, many come to hospital to whom "Youth was a blunder, Manhood a struggle, and Old Age a regret," but even they have their personal rights.

Because those intrepid sailors, the Phænicians, kept secret their methods of navigation, the Continents of the Americas, Africa, and the East remained hidden from us for some hundreds of years till methods of navigation were rediscovered, so I think it is the duty of surgeons to succeeding generations to chart their journeyings amongst the seas of disease, showing not only how, in certain waters and with certain bearings, they are able to accomplish their object in safety, but also showing those rocks on which their hopes foundered. Veau's classical treatise on the treatment of cleft palate is an ideal example. For this reason, I dare to place before you some experiences in the surgical treatment of the aged.

I have, with the help of my surgical registrar and house surgeon, reviewed the treatment of 496 consecutive patients over 65 years of age who underwent major surgical operations in six successive years. Their ages and the conditions that necessitated operation are noted in Table 1.

In the same period many operations in the younger age group were undertaken as happens in the ordinary routine of a general surgical unit. An operation mortality was taken as one that was due directly or indirectly to the operation. It is to be borne in mind that the average mortality of the populace in the age group 70 to 80 years is—males, 9.5 per cent.; females, 7.6 per cent. (Professor Stevenson), so that coincidences of expected cardiac failure coming on in the post-operative convalescence period can be expected. Despite this, a sudden cardiac failure in hospital was attributed to the operation.

The surgeon must use all his judgment in considering elderly patients. It is tissues, not years, that he is dealing with. Here the patient's general practitioner can give valuable advice. The mental outlook must be noted—a will to live and courage to bear the pain of coughing with an abdominal wound are good signs.

TABLE 1.

Major Operations.

Age	Prostate		Breast		URINARY TRACT		ACUTE APPENDIX		AMPUTATIONS	GALL BLADDER		Sтомасн		ACUTE INTESTINAL		COLON AND RECTIM	Total
65-69	 57		17		7		10		0	 22		19		14		10	 156
70-74	 73		16						6								157
75-79	 43		4		3		4		10	 7		8		15		6	 100
80	 42		1		7		4		8	 4		2		11		2	 81
90	 1										••.			1			 2
							_			_				_			
Totals	 216	•••	38	•••	22	•••	19	•••	24	 47	•••	34	•••	68	•••	<b>2</b> 8	 496

If the patient, by some minor adjustment, can be relieved of his discomfort without operation, then an operation should not be advised; for example, an old man's reducible hernia can often be controlled satisfactorily with a truss. On the other hand, an irreducible hernia or a femoral hernia is not suitable for a truss, and operation should not be denied on account of age. Pain can often be eased by alcohol injections into nerves, ganglia, or placed intrathecally as necessary.

In hospital the patient should not be too much regimented. If he has lived to 75 or over he has probably found a way of life suited to him, and it should not be too crudely changed—especially diet. But it is possible he may have been depriving himself for some years of essential vitamins, especially "C" and "B," and these should be added to his diet. Some time in hospital should be spent to get him accustomed to his surroundings, nurses and doctors, so that he can undergo, to him, the great event of his life with confidence. This period helps the surgeon better to estimate the patient's general condition; signs such as rambling at night and disorientation are bad signs, and might not have been noted before. Patients often overwork, getting their affairs straightened, before coming in for operation and are physically and mentally tired, and need a few days' rest. I think the new phase applied universally, quick on to the operating table and quick out of bed, is a retrograde step. Quick out of bed is essential in cases of amputation and fracture of the femur. The patient should be exercised and made to stand on the sound limb to help it to retain its muscular power, for much of the success of the operation will be due to a strong limb on the unaffected or remaining side.

A good clinical examination is much more revealing than a host of laboratory figures. A dry tongue may show defective renal system and hypoproteinæmia may show as albuminuria. A poor cardiovascular system may show in moist lung bases or in the pulse. In old age the vital capacity is reduced. I regard poor aeration as

the chief cause of death. Chronic bronchitis in a patient with a sound heart will not necessitate abandonment of the operation if the patient has the courage to cough after operation, even if it hurts, and the anæsthetist does not depress the respiration too much and keeps his patient well oxygenated during the operation.

For successful oxygenation the hæmoglobin must be over 60 and no patient should come to an elective operation below this figure. In a surgical emergency the hæmoglobin is the best test, for it shows if there is hæmoconcentration and shock present. The blood pressure is not a true indication of early shock.

If it is admitted that

Cardiac Output = 
$$\frac{\text{Pressure}}{\text{Resistance}} \times K$$

$$C.O. = \frac{R}{R} \times K$$

if R increases the pressure increases.

In shock R is increased due to increased viscosity of the blood following upon hæmoconcentration.

$$\therefore$$
 C.O.  $\times$  R (++) = P++ $\times$  K

so that pressure only falls when the heart is failing.

A patient may look well, have a pulse of 70-80 and a satisfactory blood pressure, yet be in the first stage of shock. This must be corrected by transfusions before any operation is undertaken. An anæsthetic and operation undertaken when shock is present may make the condition irreversible.

A patient admitted with strangulated hernia had a pulse 72, but his hæmoglobin was 120 per cent. After transfuson the hæmoglobin dropped to 96 per cent. He then stood his operation well and made a good recovery. Another patient admitted with strangulated hernia had a pulse 80 with a hæmoglobin of 115 per cent. After transfusion the hæmoglobin was reduced to 88 per cent. This patient also made a good recovery. (See Table 10 on strangulated herniæ.)

In old people with wasting there is a marked loss of peripheral vascular reserve, although the venous bed remains the same. Hence one of the causes as to why old people bear emergencies very badly as shown by the high mortality figures for these conditions. Diarrhœa is a most serious complication and must be treated energetically by transfusions and drugs as kaolin, pectinate, streptomycin, and sodabicarbonate.

In the young with trauma and shock the pulse races faster and faster, but in the old, in shock, with the markedly developed blocking at the sino-auricular node the pulse is slowed down and keeps slow, only the kick of the pulse gets more feeble, and this is followed by missed beats, a grave sign.

#### AMPUTATIONS.

The late Mr. T. S. Kirk used to teach that active bleeding and threatened gangrene were the only emergencies. Nowadays I think we can go further and say continuing hæmorrhage was the only true indication for immediate operation, the blood being restored by transfusions. We have antibiotics to control the

infection in gangrene, and operation can be planned. It is essential to wait in cases of strangulated gut to get the blood circulating volume and electrolytes restored before embarking on an operation. In gangrene of a limb a course of antibiotics will turn wet gangrene into dry gangrene and operation can then be undertaken safely. A course of antibiotics, coupled with copious fluid intake even if necessary by transfusions—will remove toxæmia, and the stumps heal better and the patient stands the operation well. Cutler (1956), who urges immediate operation, records a mortality of 38 per cent., whereas in this series with the delayed operation the mortality is 23 per cent. I see no advantage then in deep freezing of the limb with risk of poor healing of stumps. One of our aged patients, when seen, had wet gangrene extending to the junction of the upper and mid third of the thigh. He was also delirious. He was treated conservatively by antibiotics, fluids by mouth, intranvenous salines and plasma. After two weeks the gangrene area became dry and his general condition improved so that he bore amputation at the hip joint with equanimity. When last heard of, he was sitting in judgment on his fellow-citizens as a juryman.

I personally like low spinal anæsthetics, 1.2 ml. of heavy nupercaine for amputations, not high enough to lower blood pressure. Sometimes, especially in diabetic gangrene, it is only necessary to do a local amputation of toes after infection has been overcome by the use of antibiotics. If done too early, before infection is overcome the infection may extend into the fascial spaces of the sole of the foot just as occurs in the hand. In diabetic gangrene of the foot, after antibiotic treatment has overcome infection and the diabetes is controlled, a belowknee amputation is often satisfactory, but in arterio-sclerotic gangrene it is usually necessary to amputate above the knee. One must aim at healing by first intention. Guillotine operations, oblique amputations or amputations with open flaps have no place in surgery of old people; if infection is controlled they are unnecessary and unsound treatment. Old people do not stand prolonged time in bed, the flaps contract, and there is the procedure of reamputating the bone with further danger of sepsis. The flaps should contain the muscle, with the anterior flap only a little longer than the posterior one. I see no disadvantage in a pneumatic tourniquet blown up before section. Cutting the posterior flap with transfixion after outlining the flap is a great advantage, as it prevents cutting a piece of the voluminous muscle twice and interfering with the blood supply to the peripheral skin. The muscles sutured over the bone ends keep the blood vessels of the flap taut and prevent the bone end pressing too heavily against the skin. There must be no tension; the skin edges should fall together and be accurately sutured. A small drain is placed to the bone end for drainage. Care is taken in bandaging that no pressure is placed against the end of the stump. Two to four days later the patient should have two crutches and be encouraged to stand, using his good limb. If left lying long in bed his good limb gets too weak to bear him.

#### THE URINARY TRACT.

The most common condition requiring surgical treatment in old men is in the urinary tract, the enlarged prostate accounting for most of the cases. In spite of

TABLE 2.

#### AMPUTATIONS.

Ages		Number 0		DIED		CAUSE OF DEATH
					• • •	
70-74		6		2		1 Broncho Pneumonia. 1 Coronary Thrombosis.
			•••	_	•••	1 Coronary Thrombosis.
75-79	•••	10	•••	0	•••	
80+	•••	8	•••	2		{1 Broncho Pneumonia. {1 Coronary Thrombosis.
		24		4		(1 00000000)

Two patients had to have the second limb off. One died one month later (wound broke down). The other died of cerebral vascular occlusion. = 26 operations with 6 operative deaths = 23 per cent. All but two were above knee amputations. There was one amputation at hip joint. Gangrene in old age shows disintegration of the cardiovascular system, and the death rate is heavy from cardiovascular lesions in vital areas.

writings to the contrary, I have no hesitation in recommending catheterisation in acute retention. If this cannot be done aseptically in a hospital I think it is time that hospital closed its doors.

Two-stage prostatectomy is still indicated, although with modern drugs and antibiotics we can do a closed one-stage prostatectomy more frequently than in earlier days. The suprapubic cystotomy should be done with local anæsthetic infiltration. I think a better and tighter suprapubic drain is got by inserting the De Pezzer through a Kidd's cannula after exposing the bladder. The tube is correctly placed when a squirt into the catheter in the urethra is followed immediately by a flow from the suprapubic tube. The patient can then be got up without leakage and encouraged to go for short walks. The second stage is only due when the patient is fit. If in a good home he improves wonderfully, going for walks and aerating his lungs. He should open his suprapubic tube every one to two hours and connect up to a bedside bottle at night. He should drink at least three quarts of fluid per day. Tubes should be changed at least every four weeks. When due for the first change a large Foley catheter in the suprapubic wound can replace the De Pezzer. It acts efficiently and is easily replaced. A sterile safety-pin placed through it prevents it moving to and fro carrying infection into the bladder. If with a suprapubic tube the patient complains of great frequency it means that the tube is too far in, touching the trigone or else there is a severe infection with trigonitis. Altering the position of the tube will determine which. If there is leakage round the tube it means the tube is blocked. When fit, prostatectomy is carried out by low spinal anæsthesia—not higher than the pubis and by local infiltration of the suprapubic wound. A light pack is placed in the prostatic bed for twelve to twenty-four hours and a tube, the size of the index finger, placed in the bladder. The bladder is drained by syphonage—this keeps his dressings quite dry and

minimises infection. The suprapubic tube is reduced in size till the wound is practically closed. As a rule, the patient is passing water normally in three weeks. Persistent suprapubic leakage means obstruction by fibrosis or a nodule of tissue at the internal meatus. The closing stage is a dangerous time and great care is necessary that there is no obstruction to outflow and that the urine is sterile or the patient under the appropriate bacteriocidal drug.

TABLE 3.

				1	PROSTATECTOMY.
AGE		Number	DEATH	s	Cause of Death
65-69		57	 1*		Coronary Thrombosis and Uræmia.
70-74		72	 1		One-stage operation. Congestive heart failure.
75-79		43	 0		•
80+		41	 2		{1 died two weeks late of Broncho-pneumonia. 1 congestive heart failure.
90+		1	 0		(1 congestive neart failure.
		214	4		
73	• • •	1			Towns that Perset's
80		1	 0		Transurethral Resection.
		216	 4		1.9 per cent.

One-stage operation was more common in the second period as shown.

				Two-Stage		ONE-STAGE	
	1st	Period	OPERATION			OPERATION	
1st Period		1950/51/52	 Proportion	4	to	1	
2nd Period		1953/54/55	 Proportion	1	to	5.2	

\*This patient had several previous coronary infarcts and in spite of suprapubic drainage his blood urea could not be reduced below 84 mg.

An attempt was made to relieve every case of retention of urine. A number of patients were unconscious with uræmia when admitted, who ultimately went on to successful prostatectomy. Cardiac cases were not refused, as it was felt the relief of urinary retention would benefit the cardiac muscle. In these very ill patients a suprapubic drainage was done under local anæsthesia and, when the patient's general health was improved, prostatectomy performed.

In one-stage prostatectomy Millen's method has been discarded as it has been found liable to be followed by fibrous stricture at the internal orifice, and the Wilson Hey type of operation is preferred. The three-way Foley catheter is used and a continuous drip of sodium-citrate is allowed to run into the bladder for two to three days. When there is no sign of enough blood in the urine to obstruct, the catheter is removed, and the patient is usually up in five days. The urine of these cases can be kept sterile throughout. This is contrary to some statements published recently.

TABLE 4.

Other Major Operations on Urinary Tract.

			-	· · · · · · · · · · · · · · · · · · ·	,
AGE	AGE NUMBER		ER	OPERATIVE DEATHS	REMARKS.
					Recovered from operative procedure but died after two months and within four months.
65-69		7		1	
				Exploration of malignant	
				kidney	
70-74		5		·	1-Partial cystectomy and trans-
					plantation of one ureter.
75-79		3		•	1-Infected bladder and papillo-
					mata of bladder.
80		7			1-Partial cystectomy and trans-
					plantation of one ureter.
		—		. —	
To	ΓAL	<b>22</b>		1	3

### MAJOR OPERATIONS PERFORMED OTHER THAN PROSTATECTOMY.

RENAL	VESICAL	Papilloma	$\mathbf{C}_{A}$	ARCINOMA		Exploration
Calculi	Calculi	OF BLADDER	OF	Bladder	STRICTURES	OF KIDNEY
		C.		<u> </u>	_	
		C.	ystectomy	and		
		T	ransplanta	tion		
			of	Transplantati	on	
			Ureters	Ureters		
2	5	5	3	5	1	1

#### TABLE 5.

### BREASTS.

#### RADICAL MASTECTOMIES.

Age	Number		DEATHS
65-69	 17		0
70-74	 16	•••	0
75-79	 4		0
80	 1	•••	1*
	38		1

<sup>\*</sup>One anæsthetic death (hexamethonium). This patient had had a hemiplegia three years previously and had a high blood pressure. The operation was in the early days of the use of hexamethonium compounds.

Urethral resection of the prostate has been reserved for malignant cases. Double orchidectomy, leaving the epididymis, if the testicles are not atrophic, should be done as well as stillbestrol treatment.

The infiltrating carcinoma of the bladder wall in the old is at first often overlooked. In the early stages the complaint is frequency; in the male it suggests prostatic irritation and often after rectal examination and measuring residual urine the patient is reassured and given some urinary antiseptic. In the female the frequency is frequently put down to infection. Here careful vaginal examination of the base of the bladder may reveal the induration and be more easily demonstrated in this way than by the cystoscope. In the older age group the onset of persistent frequency not accounted for by infection or by a prostate raises the suspicion of an infiltrating carcinoma. Excision of the bladder or radiation of it, combined with transplantation of the ureters, at least relieves for a time. The more common carcinoma of the bladder is the adeno-carcinoma or the malignant papilloma more frequently associated with hæmaturia. The papillomata can often be kept under control for many years by diathermy through a cystoscope. These have more chance of radical cure by resection of the bladder. Old patients stand this and transplantation of the ureters well. The method of transplantation used has been a modified Coffey technique after a period of intestinal antiseptics. I have had no urinary leaks causing a mortality from this technique. Some hydronephrosis has frequently resulted from the transplantation.

Retention of urine in the aged female must be looked for. Urinary incontinence in the female, as in the male, may be just an overflow incontinence. Catheterisation is usually all that is required, but occasionally strictures of the female urethra are met with and a pessary that has been in the vagina untouched over twenty years has had to be removed.

#### RADICAL MASTECTOMY.

Radical mastectomy is well borne in the old. I still consider it is the method of choice. It leaves less disablement than a simple mastectomy if the tail of the breast is removed, and I cannot agree that the sub-scapular glands are left. In no case has there been a local recurrence which would be the case if these glands are left. Deep X-ray by an expert may be superior to a so-called radical mastectomy that is inexpertly and carelessly done. Radium and deep X-ray have their uses. I have seen better results from radium implantation than deep X-ray, but with modern apparatus and technique this may be reversed (Table 5).

#### THE GALL BLADDER AND BILE DUCTS.

On account of the poor vascularity and atrophy of muscles perforation of a viscus is more easily produced in old age, so that perforation of peptic ulcers, gall bladder and appendix is met with more frequently in the older age group.

In a series of gall bladder operations there was only one gall bladder perforation, but J. Cutler found eight perforations in twenty-eight acute cases. It is to be remembered that old people treat abdominal pains lightly and are inclined to try first home remedies like a purge, and this would hasten the perforation of a viscus. If an acute cholecystitis in an old person does not show signs of subsiding with

treatment in twenty-four hours it should be drained under local anæsthetic and thus avoid perforation with peritonitis. Cholecystectomy in the acute stage is contraindicated. Cutler gave a mortality of close on 60 per cent. for cholecystectomy in acute cases. Even with a stone in the common bile duct drainage of the gall bladder after gently extracting the stones from the gall bladder is efficient without interfering with the common bile duct. I have found this indirect drainage life-saving. Cutler stated that exploration of the common bile duct carried a mortality of 73 per cent. Many of these cases do not require a second operation and the bile channels can be easily viewed a week later by injecting radio opaque fluid into the gall bladder through the drainage tube. Severe cholæmia can be successfully treated by transfusions of glucose saline and plasma and, if infected, by adding antibiotics, varying the dose of the latter according to the renal output.

Gall stones in themselves are not an indication for operation, but an old patient who harbours gall stones and gets periodic attacks should—unless there are special contraindications—have the gall bladder removed in a quiet interval to avoid an emergency operation. It is as safe an operation in the aged as in the young.

TABLE 6.

OPERATIONS ON GALL BLADDER AND BILE DUCTS.

Age		Number		DEATHS
65-69		$\boldsymbol{22}$		,-
70-74	•••	14	•••	_
75-79	•••	7		_
80+		4	•••	-
		47		0

43 Cholecystectomies.

2 Cholecystduodenostomies

Nine of these cases had stones in common bile duct. One case had ruptured gall bladder.

#### OPERATIONS IN THE STOMACH AND DUODENUM.

A patient with a hæmatemesis operated upon after a first transfusion does comparatively well compared with a patient who has been treated more conservatively and has had several transfusions before operation is decided upon. It is a good rule that a patient who gives a history of an ulcer and who has a hæmatemesis should be operated upon after blood transfusions have restored his hæmoglobin or in any case, if, after transfusions, he does not hold his hæmoglobin after having 500 ml. blood per eight hours for twenty-four hours. Elderly patients, on account of arterio-sclerosis, are less likely to stop bleeding than a young person. Cutler states: "The patients who died were not our oldest patients nor those most afflicted with incidental ailments but rather those who bled longest." It is best to prevent, if possible, emergency surgery by treating chronic ulcers of the

<sup>1</sup> Cholecystgastrectomy.

<sup>1</sup> Cholecystostomy.

duodenum or stomach in the old by radical operation. Properly arranged, such operations reduce the mortality rather than increase it. Mielson found that 33 per cent. of deaths due to peptic ulceration were in patients over 60 years. Hæmatemesis in patients over 70 carries a mortality of 15.9 per cent. (Fraenkal and Truelove). Davey (1956) has recently published a series of thirty elective subtotal gastrectomies for chronic ulceration without a death; whereas published figures for emergency surgery in the old are in the neighbourhood of 40 per cent.

Our own figures for operations on the stomach are given in Table 7.

#### TABLE 7.

OPERATIONS ON	Stomach	AND DUODENUM.
Age		Number
65-69	•••	19
70-74		5
75-79	••	8
80+	•••	2
		34

### CHRONIC ULCERATION OF STOMACH.

14 Sub-total Gastrectomies	-	-	-	0 deaths.
1 Gastroenterostomy	-	-	-	0 ,,
_	,			
15				0 deaths.

#### EMERGENCY OPERATIONS.

			DEATHS
Perforations -	-	- 6	 1
Acute Hæmatemesis	-	- 4	 3
		10	4

#### CARCINOMA OF STOMACH.

	D	MINS	CAUSE
1 Total Gastrectomy and Splenec	tomy		
and Partial Pancreatectomy -	-	0	
1 Total Gastrectomy and Splenec	tomy		
and Partial Pancreatectomy -	-	1	Coronary Thrombosis; 7th day.
3 Sub-total Gastrectomies	-	0	, ,
3 Partial Œsophago-Gastrectomi	es -	2	Leak at anastomosis.
1 Gastro-enterostomy	-	0	
•			

DEATHS

CATTER

TOTAL 9 operations.

3 deaths.

#### ACUTE APPENDICITIS.

Acute appendicitis in the old is a grave responsibility to the surgeon. It carries a mortality of from 12 per cent. upwards. In Cutler's series it was 40 per cent.

The early pains are, as a rule, unheeded. The patient has probably tried to purge himself, with the result that, when admitted to hospital, eight out of nine are perforated with abscess formation or general peritonitis. Even when seen in the early stages the diagnosis may be difficult. There is little reaction on account of the low metabolic rate. Vomiting is unusual, the pulse rate is not above 80 per cent. and the temperature is not much raised. I consider a thermometer reading in the mouth of 98.4° a slight rise in temperature. Rigidity is not marked, but there is slight abdominal tumescence and tenderness on deep pressure are the main signs with frequently a furred tongue and fæcal smelling breath. When seen with the sudden pain of the perforation of the appendix and general peritonitis the condition may be mistaken for a perforated ulcer. Percussion of the abdomen will elicit most pain over the seat of the lesion. When a surgeon has any doubt as to whether the peritonitis is due to an ulcer perforation or an appendix he should always do a grid iron incision first. This is a life-saving measure. If it turns out to be a perforated ulcer it is a simple incision to close and no harm is done; whereas if a high abdominal incision is made and it turns out to be an appendix there is a great danger of losing the patient. The high incision gives more trouble with the chest. If the high incision has been made in a case of acute appendix it is better to start again and make a grid iron incision rather than enlarge the incision and try to drag a gangrenous appendix upwards. In ordinary circumstances appendicitis carries a higher mortality with a medial incision than with a lateral one. When the appendix is approached from the side the defensive mechanism of the omentum is not interfered with.

TABLE 8.
Acute Appendicitis.

Ages		Number		DEATHS
65-69	•••	10	•••	.1
70-74	•••	1	•••	0
75-79		4	•••	2
80	•••	4	•••	0
		19		3

Mortality 15.8 per cent.

Out of nineteen cases fifteen had already perforated—79 per cent. (Seven abscess formation; eight general peritonitis.)

History extended from twenty-four hours to two months.

#### ACUTE INTESTINAL OBSTRUCTION.

The common causes of intestinal obstruction in the older age groups are hernia, carcinoma of colon, bands, volvulus and gall stone ileus.

In the older age groups intestinal obstruction, due to malignant growths, play a large part. Obstructed and strangulated herniæ are other common causes. Intestinal bands, large gall stones and volvulus are not so common. The condition is always serious; more so if there is dilated small intestine. Obstruction confined to the large intestine does not produce shock so easily nor is it so marked.

Operation in all cases must be delayed till the blood circulating volume and electrolytes are restored to normal, even delaying operation up to twenty-four hours. As has been pointed out in a previous paper to this Society, the operation itself lowers the circulating body plasma by 10 to 15 per cent., and if it is already lowered by the obstruction it is possible to lower it to a state where it is irreversible. The hæmoglobin on admission gives a rough idea of the amount of shock. It is much more reliable than the blood pressure. Gastric suction and transfusion undertaken till the hæmoglobin is in the region of 70 to 80 per cent. will improve the condition. Local anæsthetic should be used in all external herniæ. An anæsthetist should stand by in case it is necessary to add to the local some general anæsthetic if widespread resection has to be undertaken. With local anæsthetic in intestinal obstruction there is less likelihood of regurgitation of stomach contents and chest complications.

TABLE 9.

Ages and Types of Acute Intestinal Obstruction.

Age		ARCINOM	Hernia	(	GALLSTON ILEUS	Adhesion	s	GENERALISED CARCINOMA
65-69		7	 7 (1)		. 0	 0		0
70-74		18	 6		1	 0		<b>2</b>
75-79	•••	6	 6		0	 <b>2</b>		0
80 +		3	 7		1	 0		0
90 +		0	 1	• • • •	0	 0		0
					_			
	TOTAL	s 34	27		2	<b>2</b>		2

Sixty-seven cases with twelve deaths-17.7 per cent.

Of these twelve deaths ten had advanced carcinoma, of which the obstruction was the terminal event. Four of them were beyond even any palliative procedure.

Thirty-six out of forty cases of acute intestinal obstruction were due to carcinoma of the large bowel when the external herniæ are excluded, i.e., 90 per cent. of cases of intestinal obstruction in patients over 65 years are due to carcinoma of the large bowel.

In obstruction of large intestine the most common cause is carcinoma. Thirty-five per cent. of growths of the pelvic colon are first seen as admissions with acute intestinal obstruction.

In the blown-up abdomen blind cæcostomy under local anæsthesia is a life-saving measure. If there is doubt a preliminary straight X-ray determines if the cæcum is dilated. Cæcostomy must be looked on as only a temporary expedient to deflate and should not be considered a substitute for colostomy. It only acts as a safety valve and does not produce proper drainage. It should be followed in seven to fourteen days by colostomy or resection of the affected area.

Ileo-sigmoidostomy is not reliable. For example: A patient, 80 years, had an acute intestinal obstruction due to carcinoma of the splenic flexure. An ileo-

## TABLE 10.

#### STRANGULATED HERNIÆ.

Comparison of Results, 1932-42, with 1950-55 period.

Immediate Operations, Belfast Hospitals, 1932-42					Delayed Operations and Transfusions, 1950-55			
			Ages	M	ORTALITY	ï	Ages	Mortality
								27 cases 1 death
Strangulated	Inguinal	Herniæ -	70 +	• • •	23%		70+	
			80 +		53%		to	3.7%
Strangulated	Femoral	Herniæ -	70 +		58%		10	5.1%
			80 +		71%		80+	

These figures show the benefit of delaying operation in acute intestinal obstruction till the electrolytes are restored by transfusions.

### TABLE 11.

NEW GROWTHS OF COLON AND RECTUM.

Ages	Number
65-69	 13
70-74	 24
75-79	 11
80+	 4
	52

- 34 new growths of colon and four at recto-sigmoid were admitted on account of acute intestinal obstruction;
- 21 of these were not removable, i.e., 60 per cent.

## Emergency Operations.

- 14 colectomies on acute cases with three deaths;
- 3 abdominal perineal resections done with one death (79 years).

Elective Operations on Colon and Rectum.

- 18 new growths of colon;
- 7 were not removable, i.e., 39 per cent.;
- 7 colectomies - 0 deaths;
- 4 abdominal perineal - 0 ...

## Other Operations on Large Bowel.

DISEASE	OPERATION	RESULT
Ulcerative colitis (68 years)	Complete removal of colon	 Recovery.
	and rectum in one stage.	
Diverticulitis, perforated and	Drainage and colostomy.	 Died.
peritonitis (86 years)	-	

sigmoidostomy was done. Due to effective valve action at the ileo-cæcal opening the obstruction was not relieved, and he became grossly distended two days later. He was delirious and had auricular fibrillation. Under local anæsthesia a cæcostomy was done and rapid deflation accomplished. Next day he had improved greatly and apologised for his behaviour the previous day. He continued to improve, and eight days later withstood the resection of the growth and an end-to-end anastomosis without disturbance. Here the cæcostomy was life-saving. That it is only a temporary expedient is shown by the patient, who had a distended abdomen due to a carcinoma in the pelvic colon. A cæcostomy was done. His acute symptoms were relieved, but he gradually got weaker, and four weeks later had difficulty in sitting up in bed. A colostomy was then performed. The growth was not removable. He got stronger, put on weight, and he went back to his work and worked for a further two years.

Old people stand elective colectomy or abdominal perineal resection well when properly prepared. Intestinal antiseptics not only help the healing, but are a preventive of shock. In acute volvulus of the colon a stomach tube passed per rectum and guided from above into the distended loop deflates it and simplifies the operation.

On account of the atony and poor intestinal musculature in the old, constipation is a common complaint, and patients with this complaint are frequently admitted as cases of acute intestinal obstruction and the hard masses of fæces may cause perforation, as the musculature and blood supply in the old are poor. Hard masses of fæces in the rectum may also, by irritating the mucosa, produce a type of diarrhœa and fæcal incontinence which is relieved by removing the mass. A detergent in an enema will break up the fæcal mass; dioctyl sodium sulphosussinate is suitable for this. Vitamin B complex in the form of yeast granules is the best laxative for the old. Prolapsus ani is a distressing complaint; the simple operation of Kirschner, in which a subcutaneous wire or nylon is tied around the anus tight enough to grip the index finger in the anal canal, will relieve the complaint.

The technique of any operation in the old is no different from that in the young, except that the surgeon must remember his tissues have a poorer blood supply, slower healing, and his patient will not survive any complications. There must be rigid asepsis, avoidance of crushing and bruising of tissues and meticulous apposition in sutured areas. As healing is slower, it is advisable to add linen or silk sutures to support absorbable catgut. The patient must be thoroughly prepared and often his condition can be much improved by preliminary blood transfusion. Vitamins, especially C and B, and a plentiful intake of fluids are necessary.

#### POST-OPERATIVE TREATMENT.

Shock, chest complications, thrombosis and embolism, and renal impairment are the chief dangers to be guarded against in the post-operative period. The patient's bronchial system should be sucked as dry as possible after operation. He should not be moved from the operating table till his hæmoglobin has returned to his previous normal. His breathing should be deep and voluntary. For this reason very light drugging in anæsthesia is absolutely necessary. Omnopon and

scopolamine is contra-indicated, shallow breathing brings on pulmonary collapsean old patient had an ampoule of omnopon and scopolamine as premedication for his anæsthetic. His respirations were so depressed as a result that he was sent back to the ward without being given an anæsthetic or having any operation. He developed consolidation of both bases of his lungs and took some weeks to make a recovery. Prolonged low blood pressure encourages thrombosis. The intravenous drip should be continued in a serious operation, 2000 cc's of dextrose solution is usually sufficient for the first twenty-four hours. Back in bed, he should be urged to cough within a couple of hours-and periodically made to cough. In abdominal conditions his side and lower ribs should be firmly held to ease his abdomen and so encourage a deep cough; a firm binder over the lower ribs is helpful. The urinary output is watched carefully and retention guarded against. Movements of the patient's legs, especially dorsiflexion and plantar flexion of the feet and wagging his limbs with the knees straight, are practised. Each day the calves of the limbs and the groins are palpated for tenderness and if any is elicited anti-coagulant therapy instituted. With kindness, encouragement to stimulate the patient's courage and hope, the old patient does well; indeed, he may do better than a younger patient, for the fact that he has lived to an old age shows a tough constitution, and he has probably immunised himself against many infections. The old patient may still have a worthwhile function in this world. He is tough and resilient and when he has the unfortunate experience of illness, amenable to surgical treatment, it is the responsibility of the surgeon to bring him back to health.

These six years of wandering that have been charted here this evening have been very happy ones. This has been due to a crew bound together in the same endeavour and filled with the same loyalty-loyalty to the patients. Bad or careless work by any member would have endangered the whole undertaking. Constant laborious and seemingly unnecessary details have been ever cheerfully undertaken. I should like to mention especially the Nursing Sisters and their Staffs. Many owe their lives to their self-sacrificing care; and to their compassion some owe the peace and happiness that came to them in the evening of their lives. Much is owed to the House Surgeons and Registrars who were responsible for many emergency operations and who helped to supervise the post- and pre-operative care. The skill of the anæsthetists, the late Dr. Harold Jefferson, whose early death was a great loss to us; Dr. Marjorie Pollock and Dr. McErvel had much to do with the good results. The checking and editing of the charts and figures I owe to my present Registrar, Dr. Graham, and House Surgeon, Dr. Houston. Much of the operating and overseeing of patients, here recorded, has been done by my valued colleagues, Mr. Vincent, and more recently, Mr. Dales. I was glad to be a member of such a happy crew and am grateful to them for their help.

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## Methods and Consequences of Lowering the Blood Pressure

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ONE of the more striking changes in the climate of physiological and pharmacological opinion, both in the laboratory and in the clinical field, is the interest taken in deliberately lowering blood pressure. Ten or twenty years ago a blood pressure below 100 mm. Hg. was regarded, in general, as undesirable, and the clinician would be tempted to start vigorous therapy, for instance, by blood transfusion or sympathomimetic amines. But recently two important things have happened. On the one hand, ganglion blocking agents have proved able to benefit malignant hypertension, and to do this (it seems) in proportion to their ability to reduce the blood pressure; on the other hand, lowering the blood pressure has been found useful at surgical operation, to diminish hæmorrhage and possibly to confer other advantages. One only appreciates this change of opinion if one looks back at older papers and sees, for instance, how the argument was advanced that high blood pressure in hypertension was a useful compensation, ensuring a satisfactory blood supply to organs in the presence of constricted arterioles.

Not all the fruits of the change of opinion are entirely beneficial. The blood pressure is sometimes lowered too often, too far, and too long. But such hypotension is clearly not intrinsically as dangerous as it was thought to be; and to produce it, by means which are understood and controllable, places in the hands of the clinician a therapeutic weapon of the first importance. At the same time the fashion for hypotension of one sort or another leads sometimes to failure to distinguish the means by which this hypotension is brought about. Accordingly, I want to start by some quite simple remarks "comparing and contrasting" (as examination papers have it) the various means by which a reduction of systemic blood pressure can be achieved by the use of drugs. Suppose one considers the simple cardiovascular reflex arc from various afferent nerves, through the central nervous system and out by the sympathetic outflow to arteriolar smooth muscles. First there are substances like the veratrum alkaloids; these have a fairly complex action, but a part of it at least is stimulation of vagal afferent nerves in the heart and lungs (the so-called Bezold-Jarisch effect). As a consequence of the incoming volley of impulses, the central nervous system reacts by producing a marked slowing of the heart and some peripheral vasodilation. The response is abolished

if the drug is prevented from reaching the vagal afferents, if the vagus nerves are cut, or if the central nervous system is destroyed. As a method of lowering the blood pressure it has the interesting advantage that it does not weaken the other reflexes controlling the blood pressure, so that postural hypotension does not occur. But it possesses the disadvantage that the effects of the incoming volleys on the central nervous system are not exclusively on the circulation. There is also, as with so many reflex stimulants of this type, considerable malaise, nausea, and even vomiting. It is difficult to find a dose which secures the hypotensive action wished for, without actively unpleasant side effects. This action of veratrine is shared by a number of other compounds, by heterologous serum in some animals, and perhaps by digitalis. It is an important action in principle, which may yet come to major usefulness.

A second type of action is on the central nervous system. Drugs like phenobarbitone have an honourable history for a sedative action, by which the blood pressure of a benign hypertensive may be restrained from at least the grosser fluctuations. One presumes that phenobarbitone exerts its effect by depressing the central drive on the sympathetic centres. Such a central sedative process is undoubtedly of great use in handling hypertensive patients, but it is limited by the fact that the sedative will, if given in larger doses, inevitably cloud other central activities. I am not aware of any central sedative which will produce large falls in blood pressure without producing marked central signs, or even frank anæsthesia.

Third are the drugs which interfere with the preganglionic nerves. At present these are chiefly pharmacological curiosities. The preganglionic nerves are cholinergic; and there are substances like local anæsthetics (Harvey, 1939), botulinum toxin (Burgen, et al., 1949), and a recent compound which can be regarded as or antimetabolite for acetylcholine synthesis (MacIntosh, et al., 1956), as well as changes in ionic concentration at the nerve endings (notably Ca++ lack (Harvey and MacIntosh, 1940)), all of which interfere with the nerve terminals so as to reduce the amount of acetylcholine released at the synaptic junctions in the ganglion. As a result, one obtains a block of transmission in the ganglion due to a lack of transmitter rather than an antagonism to the transmitter once released. But this type of action is obviously useless to practice at present; botulinum toxin poisons all cholinergic nerves so that a depression of autonomic outflow would only be obtained at the expense of widespread neuromuscular block; local anæsthetics are too weak and non-specific; and the change in calcium concentration required to produce the effect would throw any animal or patient into violent tetany. This is another attack which doubtless will bear fruit in the future.

The fourth type of action to consider is the one in which we are primarily interested, that of specific competitive ganglion block, whereby a drug like hexamethonium stops the acetylcholine still normally released, from exciting the ganglion cells in its usual way.

Fifth are the drugs which may interfere with the postganglionic neurone and its nerve endings. A few years ago one would have made simply formal acknowledgment of the possibility that an action might take place, but this is now more

than a possibility. There is the xylyl choline ether known as TM 10 synthesised by Hey and studied by Bain and his colleagues (Bain and Fielden, 1956) which can depress adrenaline output. Miss Vogt in Edinburgh has recently shown (Muscholl and Vogt, 1957) that reserpine can also depress adrenaline output in a rather interesting way, by depleting the neurone of its stores of the transmitter, in this case noradrenaline. Thus, although the nerve is in principle undamaged, yet it cannot release its normal amounts of sympathin because its stocks have been removed by some interference with its binding or metabolic production. It is interesting too that there are signs that morphine also can interfere with the release of transmitter at the post-ganglionic level.

Sixth, we have those drugs which can antagonize a transmitter once it has been released at the peripheral site; that is to say, drugs like dihydrærgotamine or dibenzyline at the sympathetic sites. For lowering the blood pressure, of course, the antiadrenaline drugs are of great importance, although perhaps they deserve attention chiefly for investigative purposes rather than treatment.

The last (seventh) group of actions are those where the drug concerned has a direct action on the smooth muscle of the arteriole wall, causing it to relax. Here one has in mind things such as the nitrites or acetylcholine or histamine. But they are all rather transient; and with one exception in principle, which I will discuss later, that of histamine release from the body, I am not aware yet of any particularly encouraging evidence that such drugs can be used for any length of time for lowering the blood pressure.

## THE PROOF OF GANGLION BLOCK.

Looking at the various methods of reducing the blood pressure, ganglion block offers one significant advantage. This is that the autonomic outflow can be interrupted without, on the one hand, any action of the central nervous system (such as phenobarbitone exerts) nor, on the other hand, any action on the effector organ; the latter thus retains its sensitivity to drugs like acetylcholine or adrenaline if one wants to control an excessive degree of block. But this advantage with ganglion block only exists if the blocking agent is in fact specific. To illustrate what is meant by this, and to exemplify part of the work of pharmacological research, I would like briefly to review the evidence one has to collect before ganglion block can be taken as the sole action of a particular compound. The work I am going to describe was done some years ago by Dr. Zaimis and myself (Paton and Zaimis, 1951), and it will, I am afraid, be rather vieux jeu to some of the physiologists present.

Such a drug usually comes to notice by producing a fall in blood pressure, or, during stimulation of a preganglionic sympathetic nerve (which is quite commonly done in exploratory experiments) by producing a failure of the effector response. What is recorded is that at some step between the preganglionic nerve and the final effector organ a depression of function has occurred. How are we to disentangle the various possible causes? The first analytic step is to compare the effects of stimulating the pre- and postganglionic nerves electrically. This is done on the superior cervical ganglion, using the contraction of the nictitating

membrance as a sign of ganglionic activity. First of all, you stimulate post-ganglionically. Then you stimulate through the preganglionic electrodes. During the latter you inject the drug under test, in this case hexamethonium. It produces a complete depression of the effector response, as shown by the absence of further relaxation when the stimulation is stopped. Now turn back to the postganglionic stimulation; it is as effective as ever. Return to the preganglionic trunk, it is still blocked. This shows that the drug has interfered with nothing "downstream" from the postganglionic electrodes; in other words, the muscle itself, the action of the peripheral transmitter, and its release, are all left unimpaired.

But we still have to distinguish between a drug which acts like hexamethonium and one which depresses acetylcholine release at the nerve terminals. One has to turn here to perfusion of the ganglion, so as to collect the acetylcholine released and to try whether the amount liberated by stimulation of the nerves before and during the presence of the drug being tested is changed or not. One finds that hexamethonium, even when injected in a relatively huge dose into a perfused ganglion (about the size of a pea), produces no reduction of acetylcholine output. Hence we conclude that the drug is what we are looking for in this case, something which specifically blocks ganglia by competitive antagonism with acetylcholine at the synapse.

All the work described has been done, of course, on a single ganglion. Since ganglia are known to differ considerably in their responses, it is obviously safer to conduct some tests on other ganglia. Unfortunately, one cannot do a rigorous analysis on any other preparation than the superior cervical ganglion; but good corroborative evidence can be obtained. Thus one can compare the response to stimulating the vagus nerve with the response to acetylcholine, using as test-object the rate of the heart. If the drug is a specific ganglion blocking agent it will paralyse vagal stimulation but leave the response to acetylcholine (which acts purely peripherally) quite unimpaired. It is found that hexamethonium does, in fact, behave like this. Similarly, you can compare the response to stimulating the ganglia by nicotine with the response of the blood pressure to adrenaline or to acetylcholine. Figure 1 shows such an experiment. First of all are three control responses to the three test drugs. Then in the middle panel some hexamethonium is given, producing, with a fairly small dose, a slow fall in blood pressure due to relaxation of autonomic tone. Further big doses produce no further fall, in itself a useful check that the drug does not have any further actions on the heart or circulation. Then we repeat the test drugs and find that acetylcholine can still lower the blood pressure, adrenaline can still raise it, but nicotine is now completely ineffective. You will probably have noticed that the responses to acetylcholine and adrenaline are changed, becoming prolonged, and in the case of adrenaline, increased. These, of course, are due primarily to the inactivation of the buffer nerves which normally check a rise or fall in blood pressure; when their influence is removed, then the rise or fall can be more prolonged and possibly greater.

From all this type of evidence one concludes that a drug like hexamethonium is a specific ganglion blocking agent and free of other actions.

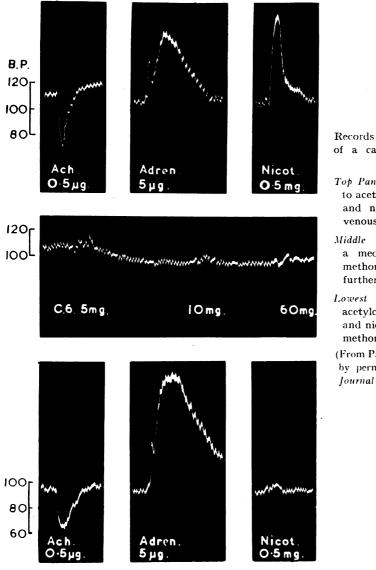


Fig. 1.

Records of the blood pressure of a cat anæsthetised with chloralose.

Top Panel: Normal responses to acetylcholine, adrenaline, and nicotine, given intravenously.

Middle Panel: Response to a medium dose of hexamethonium, followed by further large doses.

Lowest Panel: Response to acetylcholine, adrenaline, and nicotine after the hexamethonium.

(From Paton and Zaimis, 1951; by permission of the *British Journal of Pharmacology.*)

The knowledge whether a drug is specific or not is important; and I would like to mention two additional points about hexamethonium. First, one of the things that makes it specific is that it is a salt of quaternary nitrogen; without going into detail, this means that its molecules can only exist in solution carrying a positive charge—i.e., it is always fully ionised. Now such particles penetrate cell membranes only with difficulty. This gives to hexamethonium the following characteristic properties: poor absorption by mouth; distribution only in the extracellular fluid; resistance to metabolism; excretion by the kidney roughly like

inulin (neither traversing the cells of the tubules outwards in secretion, nor inwards by reabsorption); and failure to enter the cerebrospinal fluid, which is quite a sensitive test (Fig. 2). This means that any central actions of hexamethonium (and they are not strong) are excluded by permeability considerations.

Secondly, one must remember that ganglion block does not always lead to quiescence of a structure. I remember being disconcerted to see how, in the cat

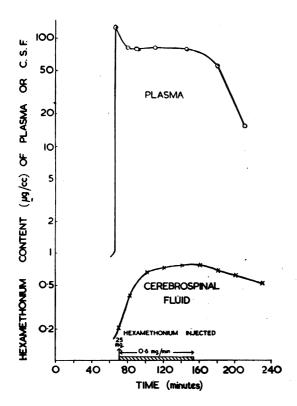


Fig. 2.

Comparison, in a cat anæsthetised with chloralose, of the concentration of hexamethonium in the cerebrospinal fluid with that in the plasma, during infusion of a large dose of hexamethonium.

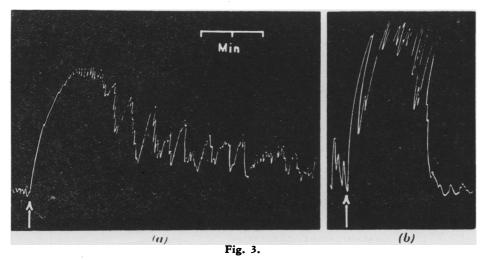
(From Paton, 1952; by permission of the Athlone Press.)

under chloralose, hexamethonium and TEA can stir up the bowel (Fig. 3) (Paton and Zaimis, 1951). But this is not a muscarinic or histaminic action; it can be closely imitated by cutting splanchnic nerves—as described by Bayliss and Starling many years ago; and is due to release of intrinsic intestinal activity from sympathetic restraint, as hexamethonium paralyses the sympathetic ganglia.

## OTHER GANGLION BLOCKING AGENTS.

Before going further, I ought to comment briefly on some of the other agents which resemble hexamethonium in action (Fig. 4). *Pentolinium* is now familiar, and resembles hexamethonium in all respects save for being more active and longer in its action. *Chlorisondamine*, likewise, is still more prolonged, possibly has a mild stimulant action on the colon, but is still like hexamethonium in principle

(Plummer, et al., 1955, 1956; Smirk and Hamilton, 1956). With mecamylamine a new element comes in. For the first time we have an active agent, not quaternary, which can be present (although only in small amounts) in the uncharged form (Baer, et al., 1956; Moyer, et al., 1956; Doyle, et al., 1956). As a result, it can penetrate membranes; it is well absorbed; it is distributed more widely than the extracellular fluid. There are hints that it may partly be metabolised. It is excreted in the urine in a rather interesting way: if the urine is acid (which increases ionization of mecamylamine in it), mecamylamine is rapidly eliminated (one supposes because it is not reabsorbed at all): if the urine is alkaline,



Cat, chloralose. Record of movements of small intestine. Intravenous injections. (a) At arrow, 0.24 mg. hexamethonium iodide per kg. (b) At arrow, 1.5 tetraethylammonium iodide per kg. (From Paton and Zaimis, 1951; by permission of the British Journal of Pharmacology.)

mecamylamine is very slowly eliminated (because now it can be reabsorbed). Thus a single circumstance (that of not being quaternary) makes oral administration convenient and duration of action controllable in principle (though it may not be worth doing in practice). One must note, however, that by the same token that mecamylamine is active by mouth, it may have an effect on the central nervous system: and it is in this direction, perhaps, which most care should be taken (cf. Doyle and Neilson, 1956).

The last blocking agent I would like to mention here is nicotine. I will not expatiate on the electrophysiological experiment which Perry and I did to study this type of action (Paton and Perry, 1953). Briefly, a drug like hexamethonium simply interferes with transmitter action—pure block; at the opposite extreme are drugs which imitate the action of the transmitter (like acetylcholine itself in excess) and, so to speak, throw the ganglion into a state of vigorous activity such that it can no longer respond to incoming signals—this is pure stimulant action. But

between these extremes is a third; where a drug begins by stimulating, i.e., imitating the transmitter, and ends by blocking it; such a drug is nicotine; and Fig. 5 (which I promise is free from any electrical symbol!) may exemplify the differences mentioned.

I have introduced nicotine because this mixed type of action runs through the whole of pharmacology; when you find that ergotamine is an adrenolytic yet contracts cerebral vessels, that drugs exhibit "tachyphylaxis," or that penicillin

Fig. 4.
Structural formulæ of some ganglion blocking agents.

MECAMYLAMINE (INVERSINE)

can sometimes stimulate the growth of organisms it usually inhibits, one is probably dealing with just this confusing but thought-promoting phenomenon.

## REDUCTION OF THE BLOOD PRESSURE BY HISTAMINE RELEASE.

I would like to introduce this by discussing another drug which has been widely used for lowering the blood pressure at surgical operation to diminish bleeding, and is reputed to be a ganglion blocking agent. This is the material usually known as Arfonad, which has now received the official name "trimetaphan." If you inject it into an animal you find that it can, indeed, paralyse ganglia and part of its action seems undoubtedly like that of hexamethonium. But if you compare,

for instance, the effect on the blood pressure in relation to that on the superior cervical ganglion (as measured by the contraction of the nictitating membrane) with similar responses obtained with hexamethonium you will see there is a considerable difference. In this particular experiment (Fig. 6) hexamethonium was able to produce a profound ganglion block; yet the blood pressure was little affected, because at the time there was little autonomic tone to be released. But Arfonad, while producing quite a long-lasting ganglion block, produced a distinct but transient change in blood pressure.

This blood pressure tracing is rather an interesting phenomenon. You can see the point of injection by a little spike (due to a momentary increase in venous

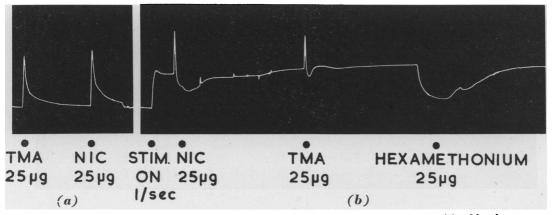


Fig. 5.—Responses of the nictitating membrane of the cat anæsthetised with chloralose.

- (a) Comparison of tetramethylammonium (T.M.A.) and nicotine given intra-arterially into the blood-supply of an unstimulated ganglion, showing comparable stimulant action by both drugs.
- (b) Comparison of nicotine, T.M.A., and hexamethonium given intra-arterially, while the ganglion is being excited by shocks at 1/second applied to the preganglionic cervical sympathetic trunk; showing the nearly pure stimulant action of T.M.A., the mixed action of nicotine, and the pure blocking action of hexamethonium.

return); then there is a latency of something like twenty seconds; finally, there is quite an abrupt but transient fall in blood pressure. This is a very characteristic example of what is called the "delayed depressor response," and it is characteristic of a group of drugs which MacIntosh and I worked on some years ago, the "histamine liberators" (MacIntosh and Paton, 1949). With many other compounds you will see the same picture with the blood pressure: the point of injection, then a latency, and then an abrupt fall followed by a recovery which depends on the dose given (Fig. 7). We found that the drugs themselves were not primarily active on the circulation; but that when they reached the tissues they released some of the histamine contained there, the histamine then circulated back in the veins, through the lungs and out again into the circulation, so that the delay in the depressor

response is simply equivalent to one circulation time. Histamine, of course, is quite a brief-acting drug, so that a histamine-liberator produces a fall in blood pressure and recovery which is not unlike that due to histamine itself, except that it is "stepped back" by the delay in the circulation time just mentioned. We proved that histamine release was occurring by showing that with a larger dose of the drug, histamine as such could be identified in the plasma.

If you inject such drugs intradermally they produce the triple response that Lewis described, a local erythema first of all which then develops into a weal with sometimes a red edge round it; and these two phenomena are accompanied

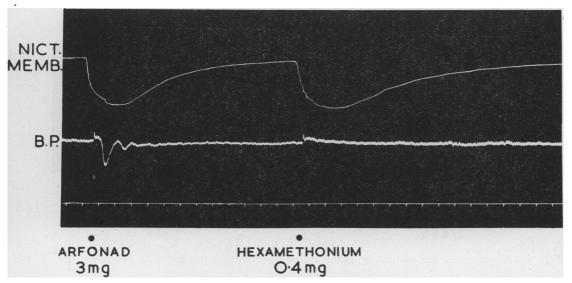


Fig. 6.—Comparison of the effect of Arfonad with that of hexamethonium (a) on transmission through the superior cervical ganglion, as tested by the response of the nictitating membrane to preganglionic stimulation at 10 shocks (second upper tracing) and (b) on the blood pressure (lower tracing) in a cat anæsthetised with chloralose. Injections are given intravenously.

by a third, the rather patchy flare extending two or three centimetres away from the point of injection. Arfonad will produce this reaction too. A decisive test for histamine release is to use cat's isolated perfused skin (Feldberg and Paton, 1951). This is a good preparation because the skin is full of histamine; yet the histamine is sufficiently firmly attached not to leak out during the handling of the skin which is involved in preparing it for perfusion. Further, you can perfuse it with a saline solution, so avoiding some awkward interfering substances present in blood. Figure 8 shows the effect of 100 µg of Arfonad in such a preparation; it releases something like 0.75 µg of histamine for each µg of Arfonad which was injected, quite a powerful release. To this we can add some of the known results reported by other people on the effects of Arfonad (Randall, et al., 1949; McCubbin and Page, 1952). Thus Arfonad (like other liberators) injected into a dog can produce profound circulatory collapse with an engorged liver, a rise in portal

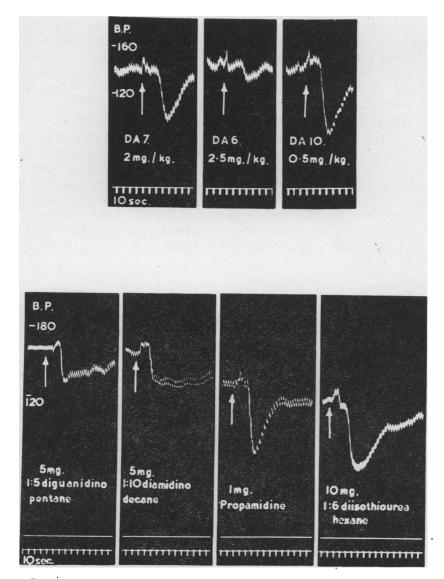


Fig. 7.—Responses of the blood pressure of the cat under chloralose to the intravenous injection of seven different histamine liberators.

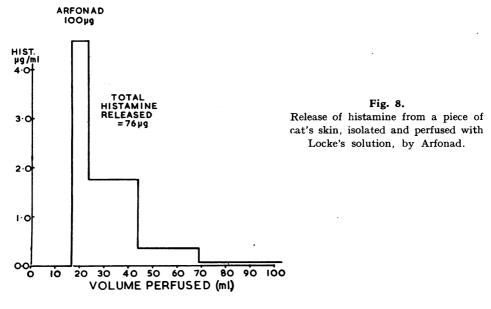
(From MacIntosh and Paton, 1949; by permission of the Journal of Physiology.)

pressure and a change in coagulability of the blood—all the symptoms of anaphylactoid shock. There seems no doubt that Arfonad can, in fact, release histamine as well as blocking ganglia.

The question arises, of course, as to whether this release occurs in man. It is quite easy to show on one's own skin that quite a dilute solution of Arfonad will produce the weal and flare response which we have already mentioned (Mitchell,

et al., 1951). Anæsthetists who look for it can see this response occurring during intravenous infusion of Arfonad; the vein and sometimes the lymphatics in the region become traced out by the urticarial response around them. Further, Payne (1955) has recently found that if you take patients receiving Arfonad and sample their gastric juice, you find that in these patients there is a definite secretion of acid gastric juice, although with patients undergoing similar operations but not receiving Arfonad the gastric juice remains more or less neutral.

One has to regard Arfonad, therefore, as possessing two distinct actions: ganglion block and histamine release. This seems to be important for understanding its action. It is often stated to be a ganglion blocking agent with a brief effect. But you will probably have noticed in the figure that in fact the duration of paralysis of the nictitating membrane it produced was really not very much shorter than that of hexamethonium, and in fact I have never been able to satisfy myself that it really is a drug of specially short action. On the other hand, if it releases histamine it might well appear to be a drug of short action;

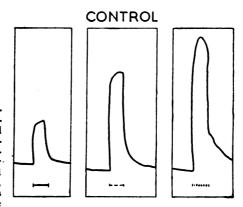


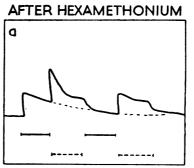
for as soon as it had completed its mobilization of tissue histamine the released histamine would be rapidly mopped up in the body, and the histaminic circulatory effects would indeed be rather transient. We have to think of Arfonad as being a drug with a potentially short action on the circulation, not because it is itself rapidly destroyed in the body, but because its action is that of histamine release on a background of ganglion block. When the infusion of drug is discontinued, the concentration of Arfonad begins to fall in the body, histamine release ceases, and the blood pressure begins to recover as the histamine is destroyed.

I have discussed Arfonad in some detail because it serves to illustrate two points. The first is that it is a neat example of a drug which, although it is a ganglion

Records of contraction of the cat's nictitating membrane excited by stimulation of the preganglionic cervical sympathetic trunk at 1, 10 or 20 shocks per second (denoted by continuous, broken and dotted lines respectively). Above are the responses to these rates of stimulation, for one minute, in a normal cat. Below are the responses obtained after hexamethonium.

Increasing the rate of stimulation in the presence of hexamethonium does not necessarily lead to a bigger postganglionic response; although the change from 1/second to 10/second in (a) does so, the further acceleration from 10/second to 20/second in (b) actually produces (after an initial augmentation) a considerable increase in block.





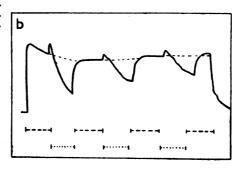


Fig. 9. (From Paton, 1952; by permission of the Athlone Press.)

blocking agent, also has another action which can contribute to its circulatory effects. It shows the importance of making quite sure that a given effect which you have identified is, in fact, enough to account for all the actions of the agent. Secondly, it has allowed me to mention to you some of the main actions of the histamine releasing process. These are, in fact, quite widely diffused over a lot of drugs (for a review, see Paton, 1957). Thus, morphine, and some of the therapeutic diamidines used in trypanosomiasis (propamidine, stilbamidine and

pentamidine) are histamine liberators. D-tubocurarine, the muscle relaxant, is quite a good histamine liberator, good enough, in fact, to be used as a standard drug for the purpose in many investigations. Strychnine, atropine and a number of other agents can also release histamine, but only in rather large doses compared to their ordinary therapeutic ones. Pethidine is a moderately active histamine liberator, and this may lie at the case of some of the urticarial responses described with it. All of these drugs can produce phenomena which look "allergic," yet need no previous sensitization, but simply the direct mobilization of the histamine locked in the mast cells of the tissues.

## FACTORS CONTROLLING THE SENSITIVITY TO GANGLION BLOCKING AGENTS.

It is a striking fact about ganglion blocking agents that patients are rather variable in their response to them. Variations up to one thousand-fold exist between the dose which sometimes will produce a distinct effect and the dose which the clinician sometimes has to use to obtain the wished-for result. The causes of this variation are several-fold. The first one is that the effect of a ganglion blocking agent depends on the activity of the ganglia on which it is acting. In part this is simply a truism. Unless there is any autonomic tone existing in the organism you will see no effect when the autonomic pathways are blocked. Indeed, it is an interesting exercise to estimate, from the response of humans to ganglion blocking agents, what autonomic activity is normally in operation. One can summarize the result in the not too seriously intended "hexamethonium man."

"He is a pink-complexioned person, except when he has stood for a long time, when he may get pale and faint. His handshake is warm and dry. He is a placid and relaxed companion; for instance, he may laugh, but he can't cry because the tears cannot come. Your rudest story will not make him blush, and the most unpleasant circumstances will fail to make him turn pale. His collars and socks stay very clean and sweet. He wears corsets and may, if you meet him out, be rather fidgety (corsets to compress his splanchnic vascular pool, fidgety to keep the venous return going from his legs). He dislikes speaking much unless helped with something to moisten his dry mouth and throat. He is long-sighted and easily blinded by bright light. The redness of his eye-balls may suggest irregular habits and, in fact, his head is rather weak. But he always behaves like a gentleman and never belches nor hiccups. He tends to get cold and keeps well wrapped up. But his health is good; he does not have chilblains and those diseases of modern civilization, hypertension and peptic ulcer, pass him by. He is thin because his appetite is modest; he never feels hunger-pains and his stomach never rumbles. He gets rather constipated so that his intake of liquid paraffin is high. As old age comes on he will suffer from retention of urine and impotence, but frequency, precipitancy, and strangury will not worry him. One is uncertain how he will end, but perhaps if he is not careful, by eating less and less and getting colder and colder, he will sink into a symptomless, hypoglycæmic coma and die, as was proposed for the universe, a peaceful entropy death."

But the position is a little more interesting still. It also appears that the ganglion blocking agent can make the ganglionic synapse more easily fatiguable.

This means that if you increase the rate of stimulation, the proportionate block begins to become greater. One obtains a ganglion which may conduct fairly well at slow rates of excitation, but at faster rates it becomes quite deeply paralysed. At the top of Fig. 9 you can see the normal response to three rates of stimulation, 1/sec. 10/sec. and 20/sec. In the middle you see the response to 1/sec. and 10/sec. in the presence of hexamethonium. Now in this particular situation at 10/sec. you are still getting some further improvement on the contraction, although much less than normally. But if 10/sec. and 20/sec. are compared, you see that as soon as you switch over to the faster rate of stimulation the ganglion becomes more deeply paralysed; return to 10/sec. it recovers; stimulated faster

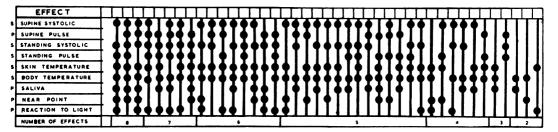


Fig. 10.—Distribution of ganglion block over nine autonomic functions in forty-one subjects. The left-hand column gives the function tested; S or P indicate whether it is sympathetically or parsympathetically controlled. On the vertical lines, one for each subject, a filled circle is given where the effect of hexamethonium 25 mg. subcutaneously exceeded a certain magnitude, for each function tested.

(From Paton and Steinberg, 1956; by permission of the British Medical Journal.)

again it becomes more deeply blocked. This has the important consequence that ganglion block will "pick out" those pathways which are being driven particularly fast, but leave those which are proceeding at a quieter rate relatively unblocked. I suspect this type of phenomenon explains some of the exaggerated responses to ganglion blocking agents which are described from time to time.

A second important factor in the sensitivity of ganglia to blocking agents is that they seem to differ in their responsiveness. In animal this is quite striking; indeed Langley more than fifty years ago first described the phenomenon with nicotine. Similarly with hexamethonium, it is much easier to paralyse the fibres to the pupil than it is the nictitating membrane. In a whole animal it is easier to paralyse salivary secretion than the activity of the vagus nerve; there are many other similar examples. The same is true in man; I would like to illustrate this with some results (Fig. 10) in an experiment which Miss Steinberg and I did at University College in a students' practical class (Paton and Steinberg, 1956). The students were arranged in teams of four with one volunteer receiving the drug (25 mg. hexamethonium s.c.) and three making systematic observations of various autonomic functions. Then we analysed the results, according to whether there had been a significant effect on particular autonomic functions studied or not, and the figure shows the results on forty-one students on which satisfactory

records were obtained. The outstanding thing about this experiment is that every student had a different pattern of autonomic block. Some would have a postural hypotension, to the verge of fainting, without any effect on the pupil or the reaction to accommodation. Others would have quite a marked effect on the eyes and yet very little effect on the blood pressure. It was remarkable that even in a single ganglion, the ciliary ganglion, you might find paralysis of the pupil and not of accommodation, or paralysis of accommodation and not of the pupil; it seemed as though you could produce a sort of Argyll-Robertson pupil or inverse Argyll-Robertson pupil according to the individual. One has therefore to allow for a substantial variation from one individual to another, and from one ganglion to another.

An analogous point is this, that it is difficult to produce complete block with these drugs. If, for instance, you give maximum doses of hexamethonium to an anæsthetised animal, you will still fail to lower its blood pressure as far as can be done by destroying the spinal cord; and there are other examples illustrating the difficulty of paralysing all the ganglia in the body. Now there is an analogous clinical situation here, in the difficulty met by the surgeon undertaking sympathectomy. There are many ganglia in the sympathetic system which are not located in the sympathetic chains normally drawn in the text books, but are hidden away in spinal nerves, in rami communicantes, sometimes found approaching the spinal canal itself (cf. Boyd and Monro, 1949). Now we know that hexamethonium, and quaternary salts like it, penetrate into the cerebrospinal fluid only with great difficulty, so that it cannot reach structures which are definitely within the cerebrospinal axis. But we know also that it can reach ganglion cells in the superior cervical ganglion, and in the heart and in the intestine, and so on. The interesting question arises as to where the barrier to diffusion of these quaternary salts disappears as you move out from the central nervous system to the peripheral nervous tissue. It seems quite possible that the change of accessibility of ganglia to compounds of this sort is not abrupt as you come through the vertebral laminæ, but may actually occur somewhere along a nerve trunk; so that any ganglion cells which have not been fully extruded into the normal sympathetic chains may, in fact, be simultaneously inaccessible, and for the same reason, not only to the surgeon's knife but also to the pharmacologist's syringe.

## THE RESPONSE TO SYMPATHECTOMY.

This brings me to a rather different topic. I mentioned that one of the surgeon's difficulties in sympathectomy is that he cannot remove all the sympathetic ganglia. It was shown quite a long time ago by Simeone, Cannon, and Rosenblueth that if you cut the majority, but not all, of the preganglionic fibres to a ganglion there is a remarkably rapid recovery of function. Recently Murray and Thompson (1957), in my laboratory, have been re-examining this phenomenon. Figure 11 illustrates what happens. Supposing you cut down the number of fibres in the preganglionic trunk of the cervical sympathetic in the neck by sectioning the rami where they leave the spinal nerves from the thoracic 1, 2, and 3 segments. This means that the remaining fibres, contributed by segments T4-7, now are the only ones

supplying the superior cervical ganglion. T1, 2, and 3 contribute about 90 per cent. of the fibres, T4-7 the remaining 10 per cent. If you stimulate the residual 10 per cent. in a normal ganglion only a small ganglionic response detectable, and electrically there is a much reduced ganglion action potential. But if you now wait for five or six weeks and then repeat the experiment, again stimulating the residual 10 per cent. coming from T4-7, you find that there is an enormous recovery of

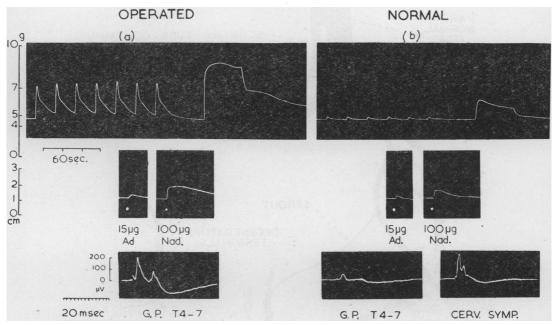


Fig. 11.—Upper Panels: Responses of the nictitating membranes of a cat anæsthetised with chloralose on (a) the operated side, on which rami T1-3 had been divided forty-nine days, previously, and on (b) the normal side. The smaller responses are due to four shocks at one shock/second delivered every minute, the larger responses to shocks at 10/second for two minutes, the shocks applied to T4-7 on both sides simultaneously.

Middle Panels: Contractions of the nictitating membranes on the two sides to intravenous adrenaline and noradrenaline, showing absence of supersensitivity on operated side.

Lowest Panels: Records of ganglion action potentials (G.P.) from another animal in which, on the operated side, rami T1-3 were cut seventy days previously. In (a) T4-7 are stimulated; in (b), first T4-7, then the whole preganglionic trunk.

(From Murray and Thompson, 1957; by permission of the Journal of Physiology.)

function. The contraction of the nictitating membrane is normal; the action potential is as large as originally.

Now the question arises as to how this return of function has taken place. Firstly, it cannot be attributed to regeneration from the sectioned rami; the time is far too short. Nor is it due to supersensitivity; this appears earlier, but it

disappears as recovery of function becomes complete; and in the figure you will see a test of the response of the nictitating membrane to adrenaline and nora-adrenaline, showing the responses hardly distinguishable from normal. So that one requires some mechanism for return of function which does not depend on regeneration of the damaged fibres nor on sensitization of the structures whose nerves have been interfered with.

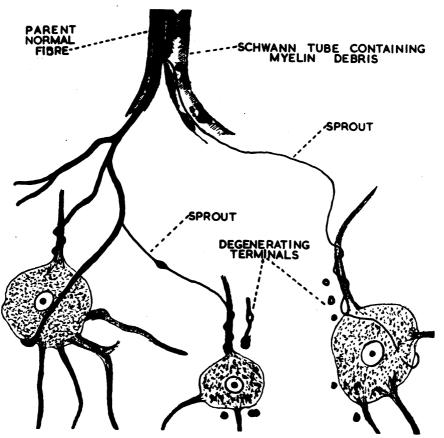


Fig. 12.—Diagram of an area of superior cervical ganglion of the cat, five days after section of rami T1-3, showing two sprouts arising from a normal parent preganglionic fibre, and typical fragments of degenerating preganglionic terminals.

(From Murray and Thompson, 1957; by permission of the Journal of Physiology.)

The answer lies in the part played in the recovery by the remaining normal fibres. These begin to give off little "sprouts" as they are called, small axoplasmic shoots which enter the Schwann tubes of the degenerating nerves. These tubes then guide the sprouts to the deprived ganglion cells and reinnervation takes place by these means. The process of sprouting is a very rapid one, and is histologically obvious within four or five days from the first section of some of the sympathetic

preganglionic fibres (Fig. 12). The efficiency of the sprouting is enormous since it can, as we have just seen, allow 10 per cent. of the fibres to restore the function of the whole.

You will probably have suspected the occurrence of a rather interesting feature of this form of response to injury. The fibres which were left behind, the residual 10 per cent., normally innervate only a particular group of ganglion cells. In the present circumstances they normally do not run to the ganglion cells supplying the pupil at all, but only to the nictitating membrane and to vascular structures and hair follicles. But if sprouts from them enter channels normally traversed by other nerve fibres they are liable to be brought into communication with ganglion cells which they do not normally touch. This is shown rather nicely by the fact that, after the process of sprouting has developed, the residual 10 per cent. of fibres now begins to be able to produce a transient dilatation of the pupil; as the sprouting develops this dilatation becomes better and better sustained and finally approaches the normal response. Thus the phenomenon brought about by sprouting is not only a return of function, but also a redirection, a "re-routing" of the autonomic nervous system, such that preganglionic fibres come to innervate additional and novel structures.

Murray and Thompson have gone into some of the other properties of these sprouted fibres, one of which I would like to mention. The synapse made by the sprouted fibres is more sensitive than usual to ganglion blocking agents. A dose of hexamethonium which normally has little effect on the nictitating contraction will have quite a substantial effect when tested against a contraction of similar height but mediated by a sprouted system. This last observation probably serves to explain one of the rather interesting results which have been reported following Sometimes surgeons have sympathectomized a patient for sympathectomy. hypertension, and found that, after a period of reduced blood-pressure, the hypertension returns, and in a time rather soon for regeneration. This is itself odd; but the situation is made odder still by finding that in these patients, in which presumably the autonomic nervous system is much reduced in importance, they are still sensitive or even hypersensitive to ganglion blocking agents. From what I said earlier, however, about the existence of accessory ganglia, you will have recognised that sympathectomy provides a happy hunting-ground for sprouting (if I may mix my metaphors). Wherever you get ganglionic pathways which are unimpaired adjacent to others which are sectioned, there will be possibility of restoration of function in the damaged fibres by sprouting from the residual ones. This may well explain the return of function after apparently successful sympathectomies. Further, the observation which Murray and Thompson made about the special sensitivity to hexamethonium would again lead one to expect that these patients, after return of function, should still be sensitive or more sensitive to such blocking agents.

There is another aspect of the sprouting story which I think will deserve a good deal of exploitation. As one looks through the field of clinical surgery in the sympathectomy field and through some of the curious physiological oddities following denervation which have been recorded, one realises that the possibility

of sprouting is a very important one to take into account. One can expect, I think, fairly confidently that sprouting of this sort may occur wherever nerves of similar types come into relationship. By this I mean that supposing a sympathetic preganglionic trunk is sectioned, if there happen to be other cholinergic nerves in the vicinity then these, as well as another sympathetic preganglionic trunk, may well sprout and establish effective connection with the ganglion cells which have been deprived of their nerves. If one takes the clinical phenomenon of gustatory sweating, for instance, it is not impossible that sprouts grow from axons normally involved in gustatory responses into the sympathetic preganglionic pathways left behind after a sympathectomy. Likewise, the Sherrington phenomenon, the Rogowicz phenomenon and the Philipeaux-Vulpian phenomenon, conditions where contractures follow the excitation of nerves which are not normally motor, may involve the ingrowth of cholinergic nerves into trunks which have been deprived of their normal nerve fibres. The more one digs below the surface among the sequelæ to operations of denervation, the more one appreciates that the sprouting of one set of intact nerve fibres into the degenerating Schwann tubes of another set is a consideration to be taken very seriously. The autonomic nervous system is extraordinary not only in the versatility of the reactions which it mediates, but also in the effectiveness of the repair process which takes place when it is damaged.

#### THE CONSEQUENCES OF LOWERING THE BLOOD PRESSURE.

I would like now to be somewhat speculative (and correspondingly vulnerable) in comparing what can be regarded as two main methods of lowering the blood pressure. On the one hand, one can take a group of procedures such as spinal anæsthesia, ganglion block, or the administration of a drug which paralyses the peripheral sympathetic terminations. By all these manœuvres one can obtain a profound fall in blood pressure, and a marked sensitivity to posture; but the circulating blood volume is normal, and there is a peripheral vasodilation. Despite the low blood pressure, blood flow to many of the organs may be normal or even increased. On the other hand one has a group of procedures which may lead to what is called "shock." This includes hæmorrhage, histamine infusion or release in large amounts, traumatising a limb or prolonged application and then release of a tourniquet, the effect of burns or the crushing of the skin or of a limb. In all these and in other cases there is a reduction of the circulating blood volume, either by frank withdrawal of blood, or by leakage of fluid into tissue spaces out of the circulation; and there is also a vigorous sympatho-adrenal response. The total result is an intense vasoconstriction, so that even though the blood pressure may be partly restored by this reaction, the blood flow to essential areas may be quite seriously cut down. It is quite clear, for instance, that after these procedures the circulation through the gut, the kidney, the liver and the skin, and possibly sometimes the heart and brain, are quite considerably reduced. There is a very curious phenomenon which occurs with the second group of reactions which does not seem to occur, or has not yet been observed with the first group of hypotensive procedures. This is the phenomenon known as "irreversible" shock, meaning by this simply that the hypotension and peripheral circulatory failure become incurable

whatever treatment you care to give; and it is liable to occur whenever the shock persists longer than a few hours. If I may be frivolous for a moment; I hope you will not think the concept of irreversible shock is a modern one. That incomparable physiologist, Jane Austen, describes it in Sophia's dying words to Laura: "Beware of fainting fits. . . . Though at the time they may be refreshing and agreeable yet believe me they will in the end, if too often repeated and at improper seasons, prove destructive to your constitution. . . . A frenzy fit is not half so pernicious."

This phase of irreversible shock is one of which a good deal of work, some of it rather uncritical, has been devoted (cf. Green, 1953). The possible causes of the irreversible phase which have been canvassed include (1) the release of vasodepressor material (identified by at least one group of workers as the material called ferritin which is involved in iron metabolism); (2) the growth of anærobic organisms in the liver with production of toxins; (3) a hypercoagulability of the blood and formation of "micro-clots" in the circulation with progressive occlusion of blood flow in lungs and elsewhere; (4) chronic tissue anoxia with liberation of unspecified toxins or local damage to cells. None of these possibilities can be either proved or excluded on the evidence at present available. But the point which I would like to make now is that all of them can be regarded as flowing from the exaggerated vasoconstriction which follows such "shock" procedures. Clostridial organisms can flourish in an ischæmic liver, blood clots form more easily in a slowly flowing stream; ischæmia of tissue certainly releases vasoactive materials.

#### ADRENALINE SHOCK.

We have then two conclusions, the first that if hypotension is produced by a method which, amongst other things, inactivates the whole sympatho-adrenal discharge, then it appears to be relatively safe for prolonged periods; but on the other hand, with other types of hypotension which this discharge is called into being and is intense, the hypotension may become irreversible. Secondly, the theories which are called into play to explain the irreversibility all seem to focus one way or another on the vasoconstriction as being the damaging factor.

I would like to mention here a third point to consider, the rather interesting and neglected phenomenon known as adrenaline shock. Continuously or massively administered adrenaline is quite dangerous. This was first recognised in the 1914-18 war and has been repeatedly confirmed (Bainbridge and Trevan, 1917; Erlanger and Gasser, 1919). If a massive dose of adrenaline was injected into the liver, for instance, a syndrome not unlike that of anaphylactic shock occurred. A very interesting study was made by Blackett, Pickering, and Wilson (1950), in which they compared the effects of infusing continuously adrenaline, noradrenaline and renin into unanæsthetised rabbits. They found that with adrenaline and noradrenaline the requirement of these hormones to produce a given blood pressure continuously rose and that when the infusion ceased the blood pressure fell abruptly and approached lethality. But this lethal process did not depend upon the height of the blood pressure or the vasoconstriction producing it, since a satisfactory hypotension could be easily maintained with renin for as long as was desired;

and when the infusion stopped the blood pressure returned quietly to normal. Later it has been found that with continued administration of adrenaline a defect of capillary permeability may appear, leading to a loss of plasma to the tissues and there may be hæmorrhages in the pericardium and in the intestine (Freeman, et al., 1941). It is clear that this danger of adrenaline shock is more intense with adrenaline than with noradrenaline. On the practical side it seems to be relatively easily avoided by using noradrenaline if an agent of this sort is required, and by seeing that when the infusion is stopped the drug is slowly tapered off and not abruptly removed. But it is significant that the continued administration of these natural substances, a thing which may well be happening during a prolonged sympathoadrenal discharge in "shock," may in fact be quite deleterious to the body. In fact one wonders whether part of the so-called irreversible stage of shock may be marked not so much by some new event to do with the shocking process, as by a development of adrenaline shock as a consequence of an overactive and too prolonged reaction to the body to the original damage.

To all this we can add a last bit of evidence which seems to be slowly becoming clear. If you subject animals to hæmorrhagic or other types of shock, corresponding to those occurring in man, they seem to survive better if their sympatho-adrenal reaction is blocked. Thus dogs treated with dibenamine may enter the irreversible stage of shock less readily (Remington, et al., 1950; Lotz, et al., 1955). Rats in which tourniquet shock is produced may survive better if treated with hexamethonium (Spoerel, 1955). There is another rather different example which is interesting; if you poison mice with anticholinesterases you find that after treatment with hexamethonium they may be protected as much as ten-fold against the poison, protection which may in fact considerably exceed that afforded by the conventional antagonist atropine (Parkes and Sacra, 1954). So there is evidence that if you remove this particular response of the body to various stressful situations, then so far from survival being impaired, it may in fact be improved. I think it is not unfair to mention too the interest taken in procedures such as cooling and ganglion block, and the use of central depressants of various sorts to make a patient more fit for various operative procedures, yet with the expressed intention of abolishing the autonomic responses.

## THE PHYSIOLOGICAL SIGNIFICANCE OF THE AUTONOMIC NERVOUS SYSTEM.

The conclusions I have just been outlining, if they are followed to a logical conclusion, produce the rather disconcerting result that the autonomic nervous system may be a substantial liability to the body, and it is this last possibility which I would like briefly to examine. The usual teaching about the sympatho-adrenal system is based on the work of Cannon and is expressed in the classical statement that it is a system which confers an advantage on the organism when it meets emergency of some sort, resulting in the need for staying to fight, or taking flight, or expressing fright. It is fairly obvious, I think, from several lines of study that the system is not essential for ordinary life. Cannon (1930) himself showed that, after the sympathetic nervous system had been ablated, a cat could still lead a relatively normal life. It is true that he probably did not remove as

much of the system as he thought, in the light of our new knowledge about accessory ganglia, but there was no doubt that he did attenuate it considerably. Similar work has been done on the dog yielding quite similar results (MacDonough, 1939).

Added to this you can consider the progress of patients who have been sympathectomised or treated with ganglion blocking agents. It is true that their activities are somewhat modified and there are a number of side actions accompanying ganglion block to which adaptation is needed. But if you think of other structures of the body such as the adrenal cortex, the pituitary gland, the kidneys, or the liver, you can immediately recognise that the autonomic nervous system does not occupy a point of comparable vital importance. One could fairly suggest that whatever the autonomic nervous system's importance may have been for some lower organism, it no longer occupies such a key position for mammalian life, or in particular for human life. Indeed, its presence may in fact confer a liability, in that it makes possible the play of emotion of all sorts of our viscera, and so gives rise, perhaps, to the psychosomatic diseases, and conditions such as peptic ulcer and hypotension in their neurogenic aspect. It is worth while to balance up mentally (though, of course, artificially) the physiological loss which would be incurred by abrogating our right to an autonomic nervous system, against the clinical gain by the number of diseases from which we would be freed.

But, of course, Cannon's view on the sympathetic was that its rôle was not in normal life but under emergency conditions. I think it is this concept particularly which has been eroded of recent years. I do not see how one could predict, if this was really true, that the inactivation of the sympathetic by dibenamine or the paralysis of autonomic ganglia by drugs should really favour survival in situations such as hæmorrhage, tourniquet shock or poisoning with anticholinesterases; or that the human organism should be more ready for elaborate and taxing surgical operation when all its autonomic defences are shattered by refrigeration and whole batteries of paralytic cocktails. One gains, instead, the impression that the autonomic system is an evolutionary heritage which, however useful in our ancestral past, now seems to be out of gear with the requirements of human social life with its continued and varied emotional pressures. This is a philosophical, and nearly untestable idea. Yet I personally find it a stimulating one, as well as one which can produce heated argument. Certainly it serves to show that we cannot, even now, give a satisfactory account of the system-not even of the reactions to a fall in blood pressure; and to remind one how much there is still to do in a field in which—as does not always happen—the pharmacologist and the surgeon can happily and profitably hunt together.

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## Labyrinthine Vascular Disorders

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## An Address to the Ulster Medical Society, 6th December, 1956

This evening I am going to talk to you about the subjects of perceptive deafness, tinnitus, and vertigo, and produce clinical evidence that in many patients perceptive deafness, tinnitus, and vertigo are due to vascular changes in the inner ear.

My own interest in these conditions commenced when I met James Seymour at the Middlesex Hospital six years ago. The stimulus which he gave me then has been the major factor in producing this paper to-night. Seymour, six years ago, knew from his clinical association with the late Garnett Passe (1945, 1951, 1953) that certain labyrinthine disorders responded to local vasodilation—either by drugs, sympathetic block, or sympathectomy. He had himself injected a case with acute labyrinthine vertigo and seen the dramatic alleviation of symptoms it Seymour has actively been investigating these disorders from the experimental and histological viewpoints since then (1953). Like Sherlock Holmes, however, he required his Watson, a clinician, interested in deafness, not hidebound by conventional theories of deafness, and with a basic training in audiometry, surgery, and scepticism. He had had some difficulty in interesting any clinician in this work until our paths crossed in 1950. It was not, however, until 1953, when I had completed the build-up of a complete otological unit at Omagh, that I was able to begin an investigation into these disorders. I had by that time discovered that inner ear symptoms were as common or commoner in Ulster as in England, and that they were no better treated. Eustachian catheterisation sedation and psychiatric consultation were still the order of the day.

In the majority of patients with these symptoms clinical examination of the ears and central nervous system proves completely negative. Further investigation can only be done by a scientific examination of the function of both cochlea and vestibule. The procedure of making a diagnosis is, of course, still essentially a clinical one, a good history being of paramount importance, but a diagnosis cannot be reached without routine audiometry, recruitment tests, and tests of vestibular function. The audiometer is as essential to the clinician dealing with deafness as the X-ray machine to the orthopædic surgeon, or the electrocardiograph to the cardiologist. The type and degree of deafness and the success or otherwise of all forms of treatment should be measured on the audiometer or by repetition of the

vestibular tests. Even eustachian catheterisation should be done under audiometric control, and assisted by the use of the nasopharyngoscope—just as ureteric catheterisation is assisted and evaluated by cystoscopic and radiological control.

Other cases with these symptoms may have associated anæmia, hypotension or hypertension. Such vascular disturbances are generalised and affect the inner ear because it is extremely sensitive to alterations in oxygen tension. In the majority of cases, however, of deafness, tinnitus, and vertigo, with or without associated nausea and vomiting, these are isolated symptoms. The blood pressure is normal, there is no anæmia, no evidence of syphilis, and no abnormal neurological findings. The abnormality is, in fact, confined to the inner ear or eighth nerve. Eighth nerve tumours do, in fact, occur, are diagnosed by application of the tests already mentioned, but are rare—probably less than 1 per cent. of cases with these symptoms. The vast majority prove to be due to an inner ear disturbance.

Frequently the sufferer gets so little help from the medical profession that, after an abortive visit or two, he keeps his less severe symptoms to himself, and only presents himself when incapacitating vertigo or severe deafness drive him to do so. Often the sufferer has a superimposed and understandable anxiety state.

I have already mentioned that inner ear symptoms are common. During the past three and a half years I have investigated approximately 350 patients—an incidence of approximately two new cases per week referred from a widely scattered area for specialist examination—the true incidence must be much higher than this. These patients have all been without visible ear pathology, and many have been young healthy adults.

Approximately 40 per cent. have perceptive deafness, tinnitus, and vertigo in varying degrees and combinations. Approximately 35 per cent. have perceptive deafness without any vestibular symptoms at all, and 18 of the remaining 25 per cent. are composed of cases of otosclerosis, congenital deafness, meningitic deafness, acoustic trauma, acoustic neuromata, traumatic labyrinthitis, deafness following mumps, etc. In the remaining 7 per cent. no diagnosis was made. Thus in 75 per cent. of cases, mostly patients in the prime of life, with inner ear symptoms, the trouble appears to be in the inner ear itself without demonstrable cause.

#### Deafness. Symptoms.

The characteristic feature in many early cases is the intermittent character of the deafness. Many patients will notice and comment upon this spontaneously and some will correlate it with seasonal or temperature changes or ascribe it to catarrh. The deafness is frequently worse in cold weather and improves during the rare warm spells we get in Tyrone and Fermanagh. One patient could induce an attack of vertigo and tinnitus by drinking very cold water. It is this seasonal fluctuation of the hearing which has created the impression that eustachian obstruction is present. Audiometry and careful clinical examination reveal that such obstruction is very rare in these cases, and that the deafness is of perceptive and not obstructive type.

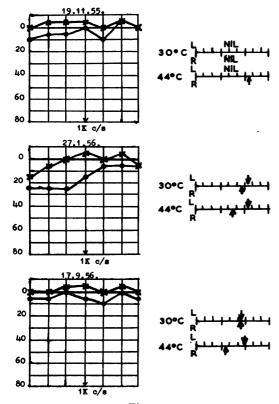


Fig. 1.

## Mrs. M. B. Age 41 years.

First seen 19/11/55.

Bilateral tinnitus for twenty years. Slight right deafness. No vertigo. Some distortion of hearing. No abnormalities in C.N.S.

Blood pressure 140/80.

Nose and throat healthy.

Left tympanic membrane normal.

Right tympanic membrane bears attic scar.

Nervous individual.

#### Diagnosis:

Early right-sided vascular inner ear lesion with progressive hearing loss.

Treatment: 7/1/56. Right stellate block.

Phenobarbitone.

#### Results:

Temporary cessation of tinnitus and sound distortion.

Restoration of normal caloric picture.

Further Treatment: 27/1/56.

Right upper dorsal sympathectomy.

#### Results:

Tinnitus reduced.

Hearing distortion relieved completely.

Hearing restored to normal.

In many patients there is also a definite progressive element about the hearing loss. The rate of progression, however, is extremely variable, and can only be assessed by repeated audiometry under standardised conditions. The rate of progression is, however, of vital importance in prognosis. As the hearing deteriorates so does the tendency to fluctuation disappear, and eventually the patient is left with a severe sustained perceptive deafness in one or both ears. I have watched this happen many times during the past five years. Many patients complaining of only slight deafness and/or tinnitus are found to have considerably reduced or absent vestibular function also (Fig. 1). In other patients there may be a very sudden usually unilateral complete loss occurring in a matter of hours or a day or two. On close questioning, the patient has usually suffered vertigo at the time he or she became deaf, but this is not often disclosed unless specifically mentioned. Two such cases are illustrated in Figs. 2 and 3. In one I was too late to do. anything—in the other you will see the effect of repeated early stellate ganglion blocks. Cases such as this should be treated as emergencies and admitted to hospital for immediate diagnosis and treatment. Many intelligent patients notice that, in addition to deafness, they also get distortion of sounds—a music teacher

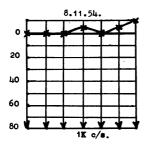


Fig. 2.

Mr. A. K. Age 26 years.

First seen 28/10/54.

Sudden onset of severe deafness right with vertigo and vomiting two months ago. Slight right tinnitus. No abnormalities in C.N.S. Ears, nose and throat healthy. Tympanic membranes normal.

Diagnosis: Sudden right cochlear death.

Treatment: 8/11/54. Right stellate block.

Results: No change after block.

Comment: Too late.

found certain notes jarring on her—a school teacher and a mother found children's voices and the wireless had altered in an unpleasant way. The distortion is commonly noticed when the threshold of sound is raised and may make loud sounds almost unbearable, and ordinary sounds uncomfortable. Distortion is almost certain evidence of positive recruitment.

#### Tinnitus.

Tinnitus is usually present. It may be very slight or so bad that it forms the patient's chief or only complaint. I agree with Passe that it is nearly always accompanied by some loss of hearing as shewn on the audiometer. I find that patients presenting with so-called idiopathic tinnitus are very rare. Vestibular hypofunction may also be present, although the patient admits to no real vertigo.

## Vertigo.

The features of aural vertigo are so well known that I will not enlarge upon them. In many patients in Tyrone and Fermanagh, however, all they will admit to is "a lightness in the head," and it is difficult to get an accurate idea of the degree of dizziness or of vertigo present. Cases of vertigo without tinnitus or deafness—the so-called "vestibular neuronitis"—are not uncommon, and tend to occur in small epidemics. The observant general practitioner is often aware of such cases and of their benign course. He can be of great assistance in observing nystagmus during an acute attack of vertigo, and I would like to pay tribute to the many practitioners in my area who have been of great help in this respect, and also to thank them for the way they have supported this investigation.

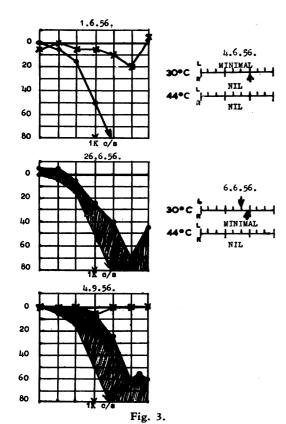
### Other Symptoms.

Patients frequently complain of a feeling of fullness on the affected side of the head, a muffled feeling, or unilateral headaches. These also are symptoms frequently falsely ascribed to eustachian incompetence.

#### Recruitment.

## SPECIAL EXAMINATIONS.

I think that it is opportune to explain here the recruitment test which appears to be ill-understood. If sound at the same frequency is led independently to each



#### Miss E. H. Age 23 years.

#### First seen 31/5/56.

Sudden onset of right deafness with a cold five days ago.

Slight right tinnitus and slight vertigo since onset.

Audiogram—severe high tone loss in right ear.

#### Diagnosis:

Sudden vascular spasm of right inner ear.

#### Treatment:

Right stellate block 1/6/56 with removal of tinnitus and vertigo and improvement in hearing. Repeated blocks caused further hearing improvement.

#### Result:

Hearing markedly improved (60 db at 2 K c/s).

Vertigo cured.

Tinnitus practically abolished.

#### Comment:

An early case. If she had been seen earlier still might well have had hearing restored to normal.

ear of the patient with unilateral deafness he will naturally hear the sound first in his good ear. If the intensity is steadily and equally raised on both sides the sound will become louder in the good ear and eventually will also rise above the threshold required in the deaf ear. Increasing the intensity still further will, however, in some cases, result in the patient saying that he hears the sound louder in the deaf ear than in the other. That is, once threshold has been reached, the deaf ear is *more* efficient than the good ear. This signifies positive recruitment and has been proved to be due to damage to the organ of Corti itself.

## Vestibular Tests.

I use the caloric testing method of Hallpike and Dix. This is a standardised procedure, using water 7° C. above and 7° C. below body temperature.

## Stellate Ganglion Block.

The other test procedure which I use extensively is a stellate ganglion block. This is not a difficult procedure, and may be of great value both in the diagnosis and treatment. During the course of this investigation Dr. Kathleen Currid and I have done some four hundred blocks, very few of which have failed to produce

Horner's syndrome and none of which has caused serious complications. The degree of vascular release after blocking is very variable. Marked flushing occurs in some individuals, whereas in others slight suffusion of the conjunctiva or tympanic membrane only results.

The first and often almost immediate effect of this procedure is that the patient finds his tinnitus reduced or absent. A single block has on occasion completely removed persistent severe tinnitus. Sensations of fullness, etc., may also rapidly disappear.

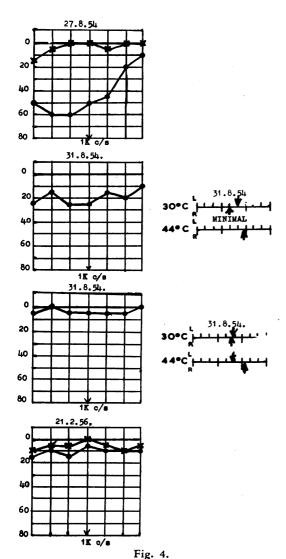
The second effect is that the hearing level on the blocked side frequently rises after twenty or thirty minutes. This rise can be demonstrated on the audiometer—It may be very marked, a twenty, thirty, or even fifty decibel improvement; more commonly it consists of a five or ten decibel rise. It very seldom shows a fall, except in cases of hypertensive deafness or in patients exhibiting markedly the phenomenon of auditory adaptation. Distortion also usually ceases temporarily after stellate block.

Stellate block is most effective, dramatic, therapeutic, and diagnostic when used during an acute attack of so-called Meniere's disease. I have been fortunate enough to be able to do this on four patients personally and Dr. Currid on two others. In most cases it is obvious which side to inject—in others study of the nystagmus, past-pointing, and hearing loss is required, but this is essentially a treatment which can be carried out in the patient's home with him in his own bed. It is, in fact, the treatment of choice of severe aural vertigo. Within a few minutes the patient, previously prostrate, may even be able to rise from his bed and the attack in all our cases has been cut short or alleviated to such an extent as to convince both the patient and the general practitioner of the efficacy of this treatment. Two cases who were having frequent attacks of vertigo prior to injection have not had a further attack for many months since injection.

In other cases of more chronic inner ear disorder repeated blocks have improved hearing, lessened tinnitus, and reduced vertigo. Some cases relapse and improve again with further blocks. I believe that in these cases sympathectomy is logically the next procedure, and I have now performed this operation by the upper dorsal route on a total of ten cases with varying but encouraging results.

#### TREATMENT.

I believe that the essence of treatment lies in realising that the time factor is of vital importance. The early case may be cured by one or more stellate blocks (Fig. 4), more advanced cases by repeated blocks or sympathectomy (Fig. 5). By cure I mean that the hearing can be restored to normal (Fig. 4) and the subor non-functioning vestibular apparatus made to function normally again (Figs. 4 and 5). For this early diagnosis is essential. Advanced cases cannot be cured by this means—the damage to the delicate end organs of the cochlea and labyrinth caused presumably by the ischæmia is permanent. They can, however, sometimes show some evidence of recovery after improvement of the blood supply (Fig. 6).



# Mrs. E. O'D. Age 55 years. First seen 27/8/54.

Recurrent dizziness nine months ago with severe vertigo two months ago lasting four to six weeks accompanied by right deafness and tinnitus. Right ear feels "full up." Blood pressure 160/90. No abnormalities in central nervous system. Ears, nose and throat healthy. Tympanic membranes normal.

## Diagnosis:

Vascular disorder of right ear with low tone hearing loss.

## Progress:

Three days later considerable spontaneous hearing improvement.

#### Treatment:

Right stellate block 31/8/54.

Recruitment test positive.

#### Result:

Further hearing improvement to within normal limits. Restoration of normal caloric picture.

#### Further Treatment:

Total of three stellate blocks done with follow up audiograms showing hearing remained well up in both ears.

#### Comment:

Lesion in right labyrinth and cochlea proved reversible. Vertigo practically abolished. Tinnitus much reduced. Hearing restored to normal.

These advanced cases may still require treatment along conventional lines such as labyrinth destruction, when the hearing loss is unilateral and severe.

The history of these cases suggests that the ischæmia is often intermittent, although the progressive element implies a gradual impairment of vascular flow superimposed upon episodes of vascular spasm. As Seymour has shown, the presence of a pre-capillary sphincteric mechanism affords anatomical evidence that such spasm can occur. The exact area of the cochlea involved explains the different patterns of hearing loss found clinically and the interference with the vestibular flow results in varying degrees of vertigo.

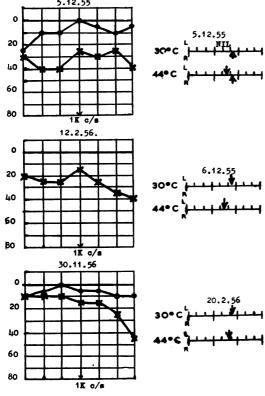


Fig. 5.

# Mr. J. M. Age 43 years. First seen 30/11/55.

Left tinnitus for one month.

Left deafness for two weeks.

Left side of head feels peculiar at times. Slight vertigo especially after drinking cold water.

No abnormalities in central nervous system.

Blood pressure 120/75.

Ears, nose and throat healthy.

Tympanic membrane normal.

#### Diagnosis:

Early vascular lesion of left inner ear.

#### Treatment:

Left stellate block 6/12/55.

#### Result:

Temporary improvement in hearing with diminution of tinnitus and loss of "peculiar" feeling.

## Further Treatment:

Left sympathectomy 13/2/56.

#### Result:

Tinnitus abolished for six months then returned.

Hearing improved.

Vertigo abolished.

Head now feels normal.

Complete cessation of cochlear flow results rapidly in cochlear death, and explains sudden otherwise inexplicable cases of deafness (Fig. 2). I have seen at least six such cases during the past three years.

I believe that emotional tension may well be a contributory factor in producing vascular spasm of this type and that this condition may therefore be classed among the psychosomatic disorders.

I believe that impairment of labyrinth circulation can occur in the child as well as the adult, and that impairment affecting the cochlea is also the main factor producing senile deafness.

Relaxation of vascular spasm should also be possible by suitable drug therapy. At the moment this is still important in a subsidiary rôle. It may well become the elective treatment with new drugs coming on the market. In my opinion, nicotinic acid is still the best drug for routine use as a vaso-dilator. I use it after a successful block and also as a palliative. Other newer vaso-dilators are at present being investigated. Priscol I found of little or no value. Antihistaminics are useful in controlling symptoms, but may, together with a heavy phenobarbitone dosage, obscure the clinical picture and alter the caloric test results.

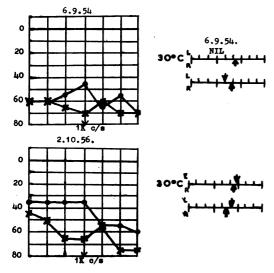


Fig. 6.

# Mr. B. B. Age 42 years.

#### First seen 26/5/54.

Recurrent attacks of tinnitus and vertigo for four years with increasing deafness L. greater than R.

No abnormalities in central nervous system.

Ears, nose and throat healthy.

Tympanic membranes normal.

#### Diagnosis:

Advanced bilateral vascular inner ear disorder.

#### Treatment:

Repeated stellate blocks done on right side with 5-10 decibel improvement in hearing each time.

Right sympathectomy 14/9/54.

#### Results:

Hearing improved.

Vertigo almost abolished.

Tinnitus much reduced.

I do not want to give the impression that every case of deafness, tinnitus, and vertigo responds to stellate block—this is far from the case. It is, however, impossible to be sure whether any individual will respond or not until it has been tried. I believe, contrary to Lewis (1956) and Spencer Harrison (1956), that stellate block is of great value both in the treatment of the early case and in deciding whether operation is justifiable.

I agree with Passe that far too little attention has been paid to the loss of hearing in these disorders; attention has been directed largely towards the tinnitus and vertigo. Progressive loss of hearing is the rule rather than the exception, and conventional treatment of a medical nature does nothing to prevent this. Figure 7 shows a typical example of a severe unilateral hearing loss, associated with attacks of vertigo, coming on over a period of five years.

#### CONCLUSION.

In conclusion, from my own investigations I believe that there is enough evidence to say that the commonest cause of deafness, tinnitus, and vertigo is vascular insufficiency, and that the title "Vascular Labyrinthine Disease" should be given to this condition. Meniere's disease forms only one clinical syndrome which can be produced by this means, and I think that this term should no longer be used.

I believe further that a new era is dawning when the physician will no longer feel that perceptive deafness is incurable; when the patient with inner ear symptoms will get a sympathetic hearing, a full investigation, and, if necessary, sympathetic surgery.

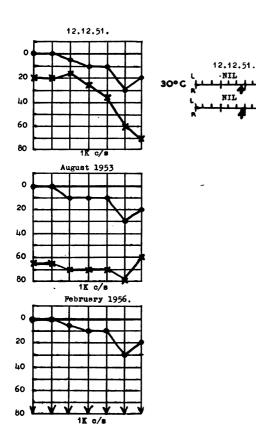


Fig. 7.

# Mr. W. McL. Age 44 years.

First seen 27/11/51.

Recent left tinnitus with some distortion of hearing and slight left deafness. Occasional bouts of vertigo—seldom severe.

No abnormalities in central nervous system. Ears, nose and throat healthy. Tympanic membranes normal. Recruitment test positive.

#### Diagnosis:

Progressive vascular lesion of left inner ear.

#### Treatment:

Medical measures.

#### Result:

Loss of all function in left ear over five years.

Many cases will continue to arrive too late for cure, many will not be suitable for this line of treatment, but, if my own experience is a guide, once it is known that an interest is taken in these disorders large numbers of patients will present themselves, some of whom it will be possible to cure of their deafness, their tinnitus, and their vertigo.

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# Prednisone and Prednisolone in the Treatment of Rheumatoid Arthritis

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Experience of the limitations of cortisone and hydrocortisone as therapeutic agents in the management of patients with rheumatoid arthritis has led to a search for newer and more potent compounds with fewer undesirable side effects. With the knowledge that the physiological properties of the adrenal steroids can be modified by relatively minor adjustments of their structural formulæ, a number of compounds have been synthesised and tried therapeutically. One of the earliest of these, 9α-fluoro-hydrocortisone acetate was tested by Boland and Headley in 1954, who found its anti-rheumatic activity to be about ten times greater than that of hydrocortisone, but unfortunately the drug had marked salt and water retaining properties which prevented its use as a practical method of treatment.

More recently prednisone and prednisolone have been synthesised. These two drugs are analogues of cortisone and hydrocortisone respectively, are derived from them, and differ only in having a double bond linkage between the first and second carbon atoms of the steroid nucleus. Bunim, Pechet, and Bollet (1955) were the first to describe their successful use in seven cases of rheumatoid arthritis, and since then further reports have followed confirming the effectiveness of both drugs (Dordick and Gluck, 1955; Margolis, Barr, Stolzer, Eisenbeis, and Martz, 1955; Hart, Clark, and Golding, 1955; and Boland, 1956). At present the general opinion held is that both substances possess an anti-rheumatic effect about three to five times greater than cortisone, and when employed in equivalent therapeutic dosage they have less sodium-retaining properties (Bunim, Pechet, and Bollet, 1955; and Nabarro, Stewart, and Walker, 1955). There is apparently little, if any, difference in the two drugs in respect of their usefulness or side effects (Bunim, Pechet, and Bollet, 1955), and Boland (1955) considered them interchangeable.

From these preliminary observations it seemed that these drugs were capable of modifying and suppressing rheumatic activity to an extent greater than any drug hitherto employed in the treatment of rheumatoid arthritis. For these reasons and because the majority of existing reports had been concerned with the short-term aspects of treatment, it was decided to carry out an extended trial of prednisone and prednisolone in a group of patients with severe and incapacitating rheumatoid arthritis. The object of the study was to discover—

- 1. The usefulness or otherwise of the drugs as a method of long-term treatment.
- 2. To evaluate the degree of improvement, objective and subjective, which could be achieved during treatment.

- 3. To discover whether long-term treatment would reveal diminishing antirheumatic activity previously observed to occur with cortisone and hydrocortisone.
- 4. To discover and assess the nature and seriousness of side effects during continued treatment.

#### Метнор.

Eleven patients with rheumatoid arthritis were treated in hospital and at a special out-patient clinic. Each was chosen for treatment because of the severity of the arthritis, or because of the failure of traditional methods to provide reasonable relief of symptoms. Initially, they were admitted to hospital, where a complete clinical examination and survey of their joints was made. Preliminary radiographs of the chest and barium meal examination of the gastro-intestinal tract were obtained in each case because of the known hazards of adrenal steroid therapy in reactivating healed pulmonary tuberculosis and producing peptic ulcers. No patient was treated who had a history of dyspepsia or who was known to have had a previous peptic ulcer.

Before starting treatment joint function was assessed. This included measurement of the circumference of the proximal interphalangeal joints (P.I.P.) with jewellers' rings; the mobility of the major joints, wrists, elbows, knees, and ankles; the maximum circumference of the knee joints; and the power of the hand grip by the patient's ability to squeeze an inflated sphygmomanometer cuff above 50 mm. of mercury. At one, three, six, and twelve months later patients were re-examined and the degree of improvement recorded as follows:—

# Grip.

Each 10 mm, increase in strength was scored as one point (+1). Where a decrease was observed a negative sign was recorded.

# Proximal Interphalangeal Joint Size.

Each P.I.P. joint was measured. The ring sizes go from A to Z and were numbered 1 to 26. The total score for the eight joints was recorded and the percentage increase or decrease noted at each examination.

# Joint Mobility.

Each 5 degree increase in joint movement over the initial angle of movement was scored as one point. Where fibrous or bony ankylosis was present movement could not be expected to improve so that, in affected patients, only the more mobile joints were measured. Three patients had their knee-joints manipulated under anæsthesia while in hospital, but the increased joint mobility obtained was excluded from the main findings.

# Knee-joint Circumference.

The maximum knee-joint circumference was measured in centimetres. Each half-centimetre (0.5 cm.) decrease in joint size was scored as -2 points. If the joint size increased a positive sign was recorded.

# The Erythrocyte Sedimentation Rate (E.S.R.).

The Westergren method was adopted and the figures obtained at the examinations are shown in the results.

# Stage and Grade of Arthritis.

This was assessed before treatment started and at the end of six and twelve months, and the degree of therapeutic response estimated in accordance with the recommendation of the American Rheumatism Association (Steinbrocker, Traeger, and Batterman, 1949).

The composition of the series of patients treated is given in Table 1.

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Case No.	Sex		Ouration Arthritis S	Stage Class	Previous Drug Therapy
1. G. R. 2. M. G.			months years		Aspirin. Aspirin, gold, corticotrophin, cortisone, phenylbutazone.
3. M. S.	F	38 11	years	IV IV	Aspirin, gold, phenylbutazone.
4. T. R.	M	64 1½	years	IV II-III	Aspirin, phenylbutazone,
5. B. I.	F	58 14	years	IV III	Aspirin, gold, pregnenolone, phenylbutazone. cortisone.
6. W. A. L. S	M	39 10	years	IV III	Gold, aspirin, corticotrophin, cortisone, phenylbutazone.
7. G. T.	M	45 6	years	IV II-III	Aspirin, gold, phenylbutazone.
8. R. J. McV.	M	50 5	years	IV IV	Aspirin, gold, phenylbutazone.
9. D. B.	<b>F.</b>	35 14	years	IV III	Aspirin, gold, codeine.
10. L. B.	<b>F</b>	49 15	years	IV III	Aspirin, codeine, phenylbutazone.
11. J. M.	F	<b>62</b> 16	years	IV III	Aspirin, gold.

The Stage refers to severity of joint involvement. Stage I early; Stage II moderate; Stage III severe with cartilage and bone destruction, joint deformity, etc., and extra articular soft tissue lesions such as nodules. Stage IV includes criteria of Stage III together with bony or fibrous ankylosis of joints. The Class refers to the patient's functional capacity. Class I complete functional capacity to carry on usual activities. Class II capacity adequate to conduct normal activities despite handicap. Class III functional activity limited. Class IV largely or wholly incapacitated; patient bedridden or confined to wheel-chair.

#### STEROID THERAPY.

Initially, all patients were given prednisolone, but on occasions prednisone was used instead, depending on supplies of each drug available in the dispensary. No differences in the effects of the two were observed, and for the purposes of this report the term prednisolone covers the use of both drugs. Treatment was started in each case with a standard amount of 30 mg. daily in four divided doses, irrespective of the severity or duration of the arthritis. The drug was then gradually reduced to an effective maintenance level. Usually within twenty-four hours there was noticeable subjective improvement, pain and stiffness easing, and the patient felt more cheerful. Objective changes lagged behind subjective improvement, although a distinct alteration could be recorded within a week or so of starting treatment. This was particularly noticeable with the return of strength to the patient's grip, but decreases in joint size and increases in joint movement took place more slowly and the maximum response was not obtained for several weeks.

#### TABLE 2.

		1.4	ADLL A	<i>.</i>				
T	th of time on manime		of 0/	) D	ا ما ما ما	lana dai		Number of Patients
_	th of time on maximi		•	_	reaniso	ione aaii	ıy.	TAILENIS
	More than 7 days	•	3 days)	-	-	-	-	1
(b)	Less than 7 days	•	-	-	-	-	-	10
Leng	th of time required	to achie	eve mai	ntenand	ce level:	s.		
(a)	Under 30 days	-	-	-	-	-	-	2
(b)	30-60 days -	-	-	-	-	<b>-</b> ,	-	7
(c)	More than 60 days	(96 and	1 88 da	ys), Cas	ses 3 a	nd 7	-	2
	tenance dose at end							
(a)	7.5 mg. daily	-	-	-	-	-	-	2
(b)	10 mg. daily	_	-	-	-	-	-	7
(c)	12.5 mg. daily	-	-		,-	-	-	2
Main	tenance dose at end	of 12 n	nonths'	treatm	ent.			
(a)	7.5 mg. daily	-	-	-	-	-	-	2
(b)	10 mg. daily	-	-	-	-	-	-	5
(c)	12.5 mg. daily	_	-	-	-	-	-	3
(d)	15 mg. daily	-	-	-	-	-	-	1
` ,	(N.B.—Cases 10 and	11 assess	ed at 11	and 10	months	respective	ely.)	
Num	ber of patients who process during m temporary or permo	aintena	nce tre	atment	and	requirin	ıg	
(a)	Requiring temporar to previous mainter	-		_			rn -	2
(b)	Requiring temporar increase in mainten	•		_	-			<b>3</b> .

The initial daily dose of prednisolone was continued for five or six days and then progressively reduced by 2.5 mg. on alternate days until 20 mg. was being given. It was held at this level for several days before further withdrawals were made. When the daily dose reached 15 or 12.5 mg. the patients were discharged from hospital. Treatment was always conservative, for it was decided to reduce the prednisolone as quickly as possible to lessen the risk of toxic effects, and, since the trial was primarily concerned with long-term aspects of treatment, general improvement in symptoms was aimed at and not complete suppression of rheumatoid activity.

During out-patient supervision the drug was further reduced to levels which kept the patient comfortable and allowed a resumption of work. Maintenance treatment varied between 7.5 mg. and 15 mg. a day with the majority of patients needing 10 mg. or less. In two patients (Cases 3 and 7) initial reduction in therapy was too rapid, and the recurrence of symptoms necessitated a temporary increase for a number of weeks before final maintenance treatment could be achieved. In four other patients symptoms increased when a daily controlling dose of 10 mg. of prednisolone was reduced to 7.5 mg. in an effort to arrive at the lowest possible maintenance level. Such symptoms occurring during the phase of prednisolone reduction were due to unmasking of the underlying rheumatoid process as a result of too rapid withdrawal of the drug or reducing it below the effective controlling dose, and were not the result of a real increase in rheumatoid activity. The occurrence, however, of a true reactivation was seen in five patients when they were on steady maintenance treatment. In two (Cases 1 and 3) a return to the original controlling dose was possible after a temporary increase, but in three others (Cases 4, 5, and 7) re-establishment of control could only be maintained by increasing the drug to levels higher than those given before reactivation took place. Details of the treatment employed are given in Table 2.

#### RESULTS.

#### Clinical Assessment.

The criteria recommended by the American Rheumatism Association (Steinbrocker, Traeger, and Batterman, 1949) to classify the severity of the arthritis, and to express the degree of improvement achieved, were adopted. The patients were assessed before treatment and at six and twelve months later, and the results recorded in Table No. 3. No alteration in the stage of the arthritic process was observed, but, as is well known, this rarely occurs particularly in patients who have established joint damage of irreversible degree. For the purpose, therefore, of evaluating clinical improvement, two variables are available for comparison. Firstly, alteration in functional capacity, and, secondly, improvement in rheumatoid activity revealed by the grade of response to treatment.

Distinct improvement in functional activity was recorded in each patient at the end of six months. Two (Cases 1 and 3) improved by two classes and the remainder by one. At twelve months this improvement was maintained in all patients except in one (Case 4), where a slight but definite lessening in functional capacity was noticed. At six months nine patients showed a Grade 2 response to treatment

TABLE 3.

		_					OF	Dise		STATE							RESPON	ISE
		Вегог		REAT	MENT					FTER	TRI	EATME			TO	TREA	TMENT	
		Activity of							Αt				At					
		Rheumatic	:					6 r	non	ths		12	moi	nths	At		At	
Са	se No.	State		Stag	e	Class	3	Stage	9	Class		Stage	•	Class	6 mon	ths	12 mon	ths
1.	G. R.	 Active		3		4		3		2				2	 Grade	2	. Grade	. 2
	M. G.	 Active		4								4				2		2
3.	M. S.	 Active		4								4			 -	2	,,	<b>2</b>
4.	T. R.	 Active		4		2-3		4		2		4		2-3	 ,,	3	,,	4
5.	B. I.	 Active		4	•••	3		4		2		4		2	 ,,	2	,,	2
6.	W. A. L. S.	 Active		4		3		4		2		4		<b>2</b>	 ,,	2	,,	<b>2</b>
7.	G. T.	 Active	• • •	4		2-3		4		2		4		2	 ,,	3	,,	2
8.	R. J. McV.	 Active	• • •	4		4		4		3		4		3	 ,,	2	,,	3
9.	D. B.	 Active		4	• • •	3		4		<b>2</b>		4		2	 ,,	<b>2</b>	,,	2
10.	L. B.	 Active	• • •	4	• • •	3		4		<b>2</b>		4		2	 ,,	2	,,	2
11.	J. M.	 Active		4		3		4		<b>2</b>		4		<b>2</b>	 ,,	2	,,	2

Grade 1 therapeutic response indicates complete remission of the disease process.

TABLE 4.

INCREASE IN STRENGTH OF HAND GRIP OVER INITIAL READING (each 10 mm. rise 1 point)—two hands scored together.

Case No.	1 month	3 months	6 months	12 months	Grade of therapeutic response at 12 months
1. G. R.	 + 30.0	+17.5	+ 32.5	+35.0	2
2. M. G.	 + 9.0	+ 8.5 .	+ 7.5	+ 3.0	2
3. M. S.	 + 2.6	+ 7.2 .	+ 7.5	+ 6.0	2
4. T. R.	 +19.0	+10.0	+11.0	- 2.5	4
5. B. I.	 +10.1	+10.7 .	+ 3.6	0.0	3
6. W. A. L. S.	 + 1.0	+ 3.6 .	+ 2.6	+ 8.5	2
7. G. R.	 + 7.3	+ 7.7	+10.3	+10.8	<b>2</b>
8. R. J. McV.	 + 2.0	+ 3.0 .	+ 2.5	0.0	3
9. D. B.	 + 20.5	+18.0 .	+10.5	+19.0	2
10. L. B.	 0.0	+ 4.0 .	+ 0.5	0.0	2
11. J. M.	 + 6.0	+10.5 .	+10.5	+10.5	2
Average all					
Patients	 + 9.7	+ 9.1	+ 9.0	+ 8.2	

Grade 2 therapeutic response indicates a major improvement.

Grade 3 therapéutic response indicates a minor improvement.

Grade 4 no improvement or progression of the disease process.

which is classified as a major improvement. In order to attain this grading the patient must show no signs of rheumatoid activity, with the exception of an elevated sedimentation rate; show resolution of articular and extra articular inflammation and reveal no signs of any new rheumatoid process. Minimal joint swelling and impairment of joint mobility associated with this swelling may, however, be present. Lesser degrees of improvement constitute a Grade 3 response or minor improvement which was shown in two patients (Cases 4 and 7). Assessment

TABLE 5.

Measurement of Finger Swelling with Jewellers' Rings

% Increase (+) and Decrease (-) Both Hands.

		,	O I	CREASE (	T) #	IND DECK	EASE	(-) boi		ade of therapeutic
Case No.		1 month		3 month	S	6 month	s	12 month	s	response at 12 months
										at 12 months
1. G. R.		- 7.0		_ 2.1		- 7.0		- 0.5		2
2. M.G.		-17.8		-13.8		-19.0		-18.0		<b>2</b>
3. M. S.		- 8.2		- 8.2		-11.8		-11.7		<b>2</b>
4. T. R.		-18.1		- 8.7		- 9.9		- 2.3		4
5. B. I.		-19.0		-19.0		-11.0		- 6.6		3
6. W.A.L.S.		-11.1		-11.0		- 4.3		- 8.0		<b>2</b>
7. G. T.		-10.3		-12.7		-12.1		- 9.8		<b>2</b>
8. R. J. McV.		- 6.8		- 1.2		+ 1.2		+ 5.4		3
9. D. B.		-13.6		-18.1		- 9.0		- 2.2		2
10. L. B.	4	* <b>-</b> 5.5		-11.0		- 3.6		<b>- 7.0</b>		<b>2</b>
11. J. M.		-10.9		-12.1		-12.5		-11.5		<b>2</b>
Average all										
Patients		-11.6		-10.6		- 9.0		-6.5		
			*(	One hand	only	recorded.				

at twelve months revealed a slight deterioration, with only eight patients making a major response, two (Cases 5 and 8) had a minor response, and one (Case 4) a Grade 4 response.

It is difficult to convey through these symbols what the figures actually meant to the patients in terms of improvement in their disability. Three patients who made a Grade 2 response were totally incapacitated before treatment. Case 1 was unable to turn over in bed and had to be fed. Cases 3 and 8 were severely crippled and unable to get out of bed unaided. After six months Case 1 was back at work as a foreman in the shipyard; Case 3 was undertaking some household duties and had taken a bus ride to visit her family doctor for the first time for several years; and Case 8 was able to walk a hundred yards and could ride a bicycle once more. In lesser degrees the improvement in strength, general well-being, cheerfulness, and freedom from pain in the other patients was most gratifying. In addition to

the general clinical assessment already described, specific measurement of various joint functions was carried out, details of which are to be found in Tables 4, 5, 6, 7, and 8.

# Strength of Grip.

A considerable increase in strength was recorded in seven patients at the end of one month. In three others the increase was slight, while in one there was no change. When the average of all the patients is taken, the greatest improvement was observed at the end of the first month, after which there was a gradual, but definite, decline at each of the subsequent examinations. Of the four patients (2, 4, 5, and 8), who at twelve months showed a loss of strength in comparison with the findings at one month, three (4, 5, and 8) had the poorest clinical response to treatment. On the whole, improvement in the strength of hand grip correlated well with the patient's therapeutic response.

TABLE 6.

Measurement of Joint Mobility to Show Increase (+) or Decrease (-) in Movement compared with Initial Reading—(each 5° one point).

Cas	se No.		Joints easured	1	month	3	mont	hs	6 mo	nths	12	mont		of therapeutic response 12 months
1.	G. R.	Е	lbows		+16		+1	8	. +	20		+14		2
2.	M. G.	E	lbows		+ 4		+	5	. +	3		+ 5		<b>2</b>
3.	M. S.	E	Vrists Ibows Inees	•••	+12	•••	+1	Ο	. +	11		+12	•••	2
4.	T. R.	V	Vrists Inees	•••	+14		+	2	. +	8		-11	•••	4
5.	B. I.	E	Vrists Ibows Inees		+11	•••	+	7	. +	2	•••	+ 8		3
6.	W. A. L. S.	E	Vrists Ibows Inees		+ 1		+	8	. –	2		+ 3		2
7.	G. T.	E K	Vrists Obows Onees Onkles	•••	+11	•••	+	4	. +	16	•••	+16	•••	2
8.	R. J. McV.	K	Inees		+ 3		+	2	. +	1		+ 1		3
	L. B.	K	Inees		_		+1	2	. +	9		+17		<b>2</b>
11.	J. M.	K	nees		+ 1		+	3		0		0		<b>2</b>
Ave	rage all													
$\mathbf{P}_{i}$	atients				+8.2		+7.	1	. +(	8.6		+6.5		

# Proximal Interphalangeal Joints.

At one month finger-joint swelling had diminished in all by 19 to 5.5 per cent. The average decrease in joint size fell during the twelve months from an initial reduction of 11.6 per cent. to 6.5 per cent. When the figures at twelve months are compared with those at one month, five patients (1, 4, 5, 8, 9) show an actual increase in joint size varying from 6.5 per cent. (Case 1) to 15.8 per cent. (Case 4). Three of these (4, 5, 8) had a poor therapeutic response, whereas two (1, 9) were classed as showing major improvement.

TABLE 7.

CIRCUMFERENCE OF KNEE-JOINT TO SHOW INCREASE (+)

OR DECREASE (-) IN SIZE

(each 0.5 cm. decrease (-) two points).

Case No.	me	re treatm	nt 1 month 3 months 6 months 12 months	e of therapeutic response t 12 months
1. G. R.	•••	73.0	1018 1 + 5	2
2. M.G.		87.7	$\dots -22 \dots -20 \dots -16 \dots -18 \dots$	<b>2</b>
3. M. S.		62.0	$\dots - 8 \dots + 6 \dots -14 \dots +13 \dots$	<b>2</b>
4. T. R.		74.2	$\dots - 8 \dots - 2 \dots - 4 \dots - 9 \dots$	4
5. B. I.		81.5	$\dots + 9 \dots 0 \dots + 5 \dots - 6 \dots$	3
6. W. A. L. S.		73.0	$\dots$ - 3 $\dots$ 0 $\dots$ + 2 $\dots$ + 2 $\dots$	2
7. G. T.	• • •	79.0	$\dots - 6 \dots - 8 \dots - 10 \dots - 4 \dots$	<b>2</b>
8. R. J. McV.		66.0	$\dots$ 0 $\dots$ + 4 $\dots$ +10 $\dots$ +10 $\dots$	3
9. D. B.		71.8	$\dots -12 \dots +10 \dots +26 \dots +18 \dots$	<b>2</b>
10. L. B.		77.2	$\dots$ + 2 $\dots$ + 2 $\dots$ - 1 $\dots$ + 1 $\dots$	<b>2</b>
11. J. M.		67.2	$\dots$ - 2 $\dots$ + 10 $\dots$ + 10 $\dots$ + 10 $\dots$	2
Overall Decreas	se			
or Increase a	ıll			
Patients	•••		$\dots$ -60 $\dots$ -16 $\dots$ + 9 $\dots$ +20 $\dots$	

# Joint Mobility.

This increased in all patients assessed at one month, but thereafter individual patients varied, some gaining further increases while others showed a reduction. The average improvement for all patients, however, declined slightly over the twelve months of observation. The most pronounced deterioration took place in Case No. 4, but when the individual figures for the other patients are studied there is little variation between the assessments at one and twelve months.

# Knee-joint Circumference.

The majority of patients, except Cases 5 and 10, showed a decrease in knee-joint circumference at one month, but at three months only four (1, 2, 4, 7) had a reduction in swelling. The overall improvement for all patients observed at one month was thus converted into an overall increase in joint size at nine and twelve

months, which may be a reflection of the additional strain imposed on these joints by the patients' greater mobility and activity. It is of interest that Case 4 and Case 5, both of whom showed a poor therapeutic response to treatment, had a reduction in knee-joint circumference at twelve months. It is difficult to explain this finding, but it may, in part, be related to increase in rheumatoid activity reducing functional use of the joint and thereby limiting swelling.

# The Erythrocyte Sedimentation Rate.

The E.S.R. was 15 mm. in one hour or more in nine patients before the trial started. Of the two with a normal E.S.R., one (Case 2) was receiving a daily suppressive dose of 67.5 mg. of cortisone acetate, when the reading was made.

TABLE 8.

ERYTHROCYTE SEDIMENTATION RATE

Са	se No.	Grade of therapeu Before 1 month 3 months 6 months 12 months response treatment at 12 months												
1.	G. R.		94		24		37		10		61		2	
2.	M. G.		14		35		_		39		37		<b>2</b>	
3.	M. S.		25		6				9		15		<b>2</b>	
4.	T. R.		95		33		64		44		58		4	
<b>5.</b>	B. I.		31		22		_		40		16		3	
6.	W. A. L. S.		20	·	5		4		13		10		<b>2</b>	
7.	G. T.	•••	<b>2</b> 8	٠	10		_		8		9		2	
8.	R. J. McV.		77		3		14		34		27		3	
9.	D. B.		9		3		3		3		6		2	
10.	L. B.		65		2		18		20		17		<b>2</b>	
11.	J. M.		15				3		14		12		<b>2</b>	
Ave	rage all													
P	atients		44		14.3		20.4		21.2		24.3			

The most marked fall in the E.S.R. was seen at one month, but thereafter the average rose during the remainder of the trial from 14.3 mm. in one hour to 24.3 mm.

# SIDE-EFFECTS OF PREDNISOLONE TREATMENT.

With the exception of the occurrence of peptic ulceration in one patient which is described in detail below, unpleasant side-effects of prednisolone therapy were slight and consisted of relatively trivial symptoms which the patients readily accepted in exchange for the benefits achieved by treatment (Table 9). Rounding of the face was seen in all, and was usually apparent within two-three months of starting prednisolone. Although less pronounced, it assumed the characteristic configuration seen in Cushing's Syndrome, and seemed to occur more easily with prednisolone than in those who were previously treated with cortisone. Four female patients (3, 5, 9, and 10) had facial flushing in addition to the "Cushingoid"

facies, which resembled the flushes associated with the menopause, but there was the additional complaint of a constantly hot and burning sensation. In one patient this was a troublesome feature for some months until it ceased spontaneously. It is unlikely that this symptom is related to secondary ovarian depression induced by prednisolone since Case 9 became pregnant while receiving the drug and Case 5 had had a normal menopause ten years before. It is probably the result of a direct vasomotor response induced by the drug. An increase in facial hair growth was observed in one patient (Case 5); it was of fine texture and caused no special complaint. A gain in weight was recorded in nine patients, ranging from 20 lb. to  $3\frac{1}{2}$  lb. One patient lost 12 lb. on a restricted carbohydrate diet, while the weight of the other patient remained unchanged. Four patients were seriously underweight before treatment started and regained their normal weight, but in

# TABLE 9.

SIDE-EFFECTS OF PREDNISOLONE TREATMENT				No. of Patients
Facial rounding	-	-	-	11
Facial flushing	-	-	-	4
Increased facial hair growth	-	-	-	1
Excessive gain in weight	-	-	-	5
Dyspepsia—negative X-ray	-	-	-	2
Peptic ulcer	-	-	-	1

five there was an excessive increase which represents a disadvantage of prednisolone therapy especially in a condition such as rheumatoid arthritis. The increased appetite induced by treatment, coupled with the metabolic effects of steroid therapy, while advantageous in wasted patients, must be carefully observed in those whose weights are normal, and excessive gains checked. No alterations in electrolyte or water metabolism were seen during the period of observation and no patient had glycosuria, hypertension or mental disturbances as the result of treatment.

# Dyspepsia and Peptic Ulceration.

Hitherto the most serious complications of prednisolone therapy has been the occurrence of peptic ulceration. Bollet, Black, and Bunim (1955) observed a peptic ulcer in three out of eighteen cases treated with prednisone and prednisolone, and stated that there was no apparent relationship between the duration of treatment or total dose of the drug and the appearance of the ulcer. With this danger in view, all patients had a preliminary barium meal examination of the stomach and duodenum before starting treatment, and at intervals throughout the trial, and, with the exception of Case No. 1, no ulceration was observed. As a precautionary measure, however, patients were advised to take a modified peptic ulcer type diet, an antacid tablet between meals, and the prednisolone after food. During treatment two patients developed mild dyspepsia, but without X-ray evidence of peptic ulceration, and the symptoms subsided rapidly without additional therapy or alteration in prednisolone dosage.

In Case 1 treatment was inadvertently started thirty-six hours before the result of the barium meal examination was received in the ward. This radiograph showed the appearance of a moderate-sized ulcer crater on the posterior wall of the body of the stomach. The decision to continue prednisolone therapy was made, in spite of the risk involved, because of the severity of the arthritis, and because it was felt that the withdrawal of prednisolone in the early stage of clinical remission would have provided a severe blow to his morale. Strict anti-ulcer treatment was therefore given in addition to the prednisolone and a special watch kept on his clinical condition. One month later gastroscopy was performed by Professor H. W. Rodgers, who reported that there was no evidence, direct or indirect, of a gastric ulcer, in the area, in which a typical ulcer showed on the X-ray. A depression in the mucosa, without converging folds, was seen to be surrounded by a low wall of folded mucosa which might have accounted for the radiological appearances. Treatment was therefore continued with greater confidence, but in February, 1956, five months after treatment started, a routine barium meal revealed the presence of a symptomless duodenal ulcer. After two weeks in-patient treatment there was radiological evidence of healing and no further dyspepsia or peptic ulceration was observed during the remainder of the trial.

#### DISCUSSION.

The results achieved during the trial clearly demonstrate that prednisolone is an effective suppressive agent for the treatment of rheumatoid arthritis. This was particularly evident in those patients who had previous treatment with cortisone, for it appeared that prednisolone possessed the advantage of re-establishing control of symptoms in those who were no longer responding adequately to cortisone. Two patients had greater relief of symptoms with 12.5 and 10 mg. of prednisolone when 67.5 and 50 mg. of cortisone respectively had been inadequate, and the three patients who had experience of both drugs were convinced of the superior results achieved with prednisolone. The improvement observed in strength and functional activity and freedom from pain has already been mentioned, and this was matched by objective evidence of increased joint function. Although complete suppression of rheumatoid activity was not aimed at, the majority of patients made a Grade 2 response to treatment, and this probably represents the best that can be achieved by any drug which is not curative.

The action of prednisolone is comparable with cortisone, and while its initial results may appear superior, evidence of its diminishing activity during the trial was obtained, which shows it possesses the same disadvantage of waning anti-rheumatic activity previously experienced with cortisone. This was apparent in the reactivation of the arthritic process which occurred in five patients, in three of whom additional amounts of prednisolone were required to maintain control thereafter. A similar finding was reported by Boland (1956).

Adverse reactions to prednisolone were, with the exception of peptic ulceration in one patient, mild and did not interfere with treatment. While facial rounding and flushing seem to occur more readily with prednisolone than with cortisone, the absence of hypertension and water and electrolyte disturbances is an advantage

which the newer steroids possess over cortisone and hydrocortisone. The occurrence of dyspepsia and peptic ulceration in patients receiving prednisolone had already been referred to, and from evidence available this complication warrants special attention. Boland (1956) reported dyspepsia occurring in five patients, two of whom had duodenal ulcers, in a series of thirty-two patients treated with prednisolone for periods up to nine months. In a further seventy patients changed to prednisolone after prolonged hydrocortisone treatment the incidence of dyspepsia and ulceration increased from 7 per cent. to 37 per cent. In this series one patient developed a duodenal ulcer during treatment, and satisfactory healing was achieved with no alteration of prednisolone therapy. The fact that the ulcer can be symptomless is an additional hazard and emphasises the importance of supplementing steroid therapy with a modified peptic ulcer diet, antacids, and the post-prandial administration of the drug in an endeavour to avoid this complication. Whether these measures are useful in preventing hæmorrhage or perforation is uncertain, but they certainly did not prevent the occurrence of ulceration in this patient. As pointed out in a recent leading article in the British Medical Journal, a controlled trial to assess the value of antacids in preventing gastro-duodenal complications is urgently needed.

Prednisolone, like cortisone, suppresses endogenous adreno-cortical activity (Nabarro, Stewart and Walker, 1955), so that it must be remembered that abrupt termination of treatment will result in symptoms of adrenal insufficiency and patients should be warned of this danger and have an adequate supply of the drug if they leave home. The importance, too, of temporarily increasing the dose during a complicating illness or operation needs stressing. If treatment has to be stopped it should be done gradually and the adrenal cortex stimulated by corticotrophin which should overlap the final doses of prednisolone.

The knowledge that prednisolone is effective in suppressing the activity of rheumatoid arthritis focuses attention on the selection of patients who are suitable for treatment. This potent drug is unnecessary when the disease is mild and responding to other well-tried measures. However, for those whose disease is progressive so that severe crippling seems to be the likely end result, it appears justifiable to use prednisolone in the hope that a remission may occur before irreversible joint damage takes place. Those most likely to benefit are in the younger and middle-age groups with severe disease of relatively recent onset and where the disease is progressive and uninfluenced by standard methods of treatment. Even in long-standing cases, however, considerable benefit may be obtained, as shown by some of the patients in this series. When the decision to undertake treatment is made the patient must be made aware of the limitations of therapy and the necessity of carrying out strictly the measures adopted for his safety.

### SUMMARY.

A clinical trial in which eleven patients were treated with prednisolone for one year is described. Measurement of joint function was made before treatment started and at one, three, six, and twelve months thereafter, and the results recorded. Improvement was most marked at one and three months, following

which a gradual deterioration took place. Nine patients showed a Grade 2 or major therapeutic response to treatment at six months, and eight remained in this category at twelve months. The occurrence of peptic ulceration in one patient, which, however, healed without alteration in the dose of prednisolone, was the only serious complication. Minor undesirable side-effects, consisting of facial rounding in all eleven patients, facial flushing in four, increased hair growth in one and excessive gain in weight in five, were observed, but did not interfere with treatment.

It is concluded that prednisone and prednisolone are effective suppressive agents in rheumatoid arthritis, and can be used beneficially for long periods in suitable patients. Both drugs possess one of the inherent defects of cortisone and hydrocortisone, and reveal in some cases a gradual decline in anti-rheumatic activity when treatment has continued for a number of months. Because these drugs appear to increase the incidence of dyspepsia and peptic ulceration, special measures designed to limit these complications should be taken routinely during their administration.

My thanks are due to Professor H. W. Rodgers, O.B.E., F.R.C.S., for the gastroscopic examination of Case 1. Initial supplies of prednisolone were provided by Dr. A. M. Brunton of Pfizer Ltd., and Mr. R. G. Kenny of Upjohn of England Ltd., and it is a pleasure to record my appreciation of their assistance.

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# WERNER'S SYNDROME

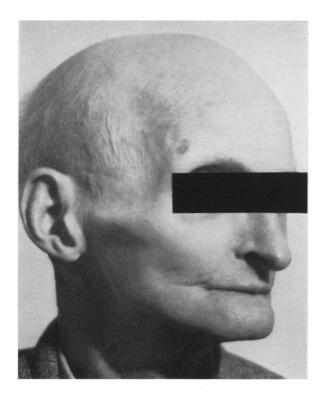
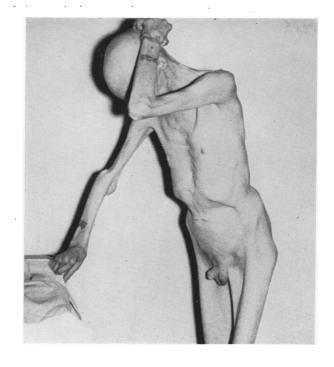


Fig. 1.

Face.—Bird-like appearance, with baldness and premature senility.

Fig. 2.

Physique.—Body relatively well-nourished compared to marked atrophy of the limbs. Atrophy of the genitals.



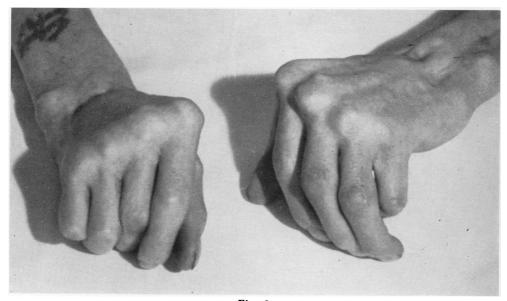
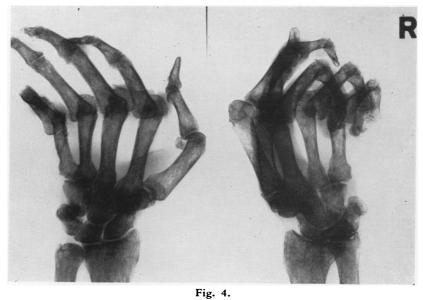


Fig. 3.

Hands.—Marked atrophy of the skin, with ulnar and flexion deformity.



X-ray Hands.—Marked osteoporosis, with arthritis and deposits of calcium.

# Werner's Syndrome (Progeria in the Adult)

# By Alan P. Grant, M.D., F.R.C.P.I. Belfast City Hospital

This syndrome, a generalised abiotrophy involving the whole body, was originally described by Werner in 1904 under the title, "Cataract in Connection with Scleroderma." The condition had occurred in four brothers and sisters. It was associated with presentility, cataracts, atrophic appearance of the skin, and ulceration of the legs which appeared between the second and third decades of life. In a review of the literature up to 1953 Irwin and Ward collected fifty-seven cases, including two of their own. They summarised the characteristics of the syndrome, which are listed below:—

- (1) Premature senility.—Premature grey hair (canities), premature baldness, atrophy of the skin, weak high-pitched voice, arteriosclerosis, early cataracts.
- (2) Scleroderma-like changes.—Atrophy of the skin and subcutaneous tissues with circumscribed hyperkeratosis. Skin tight over the feet. Ulcers over malleoli, heels, toes, and Achilles tendon.
- (3) Characteristic habitus and stature.—Short stature beginning in adolescence, beak-shaped nose, slender extremities.
- (4) Other manifestations.—Tendency to diabetes mellitus, hypogonadism, osteoporosis, localised calcification, tendency to occur in siblings.

Illustrative of the foregoing is the case to be reported here. It is a condition which does not appear to be well recognised in these islands, and it is probably commoner than the literature would suggest. Williams, in 1949, reported the only British case recognised as such which we can trace, although this is apparently the second patient from Belfast. The first was discussed by Beath in 1934 under the title, "A Case of Calcinosis Universalis with Premature Senility," and this was probably Werner's syndrome, although the patient lacked cataracts.

#### CASE RECORD.

A man aged 62 years was admitted in May, 1956, complaining of weakness, coldness, and an inflamed area on the left knee and the left heel.

There was no definite family history suggestive of endocrine disease. His father was killed in 1914 in the Army, his mother died as a young woman, he had two normal sisters and one normal brother.

The symptoms will be reviewed chronologically, although the patient was rather uncertain when his various complaints had actually commenced.

He does not appear to have been backward at school. He then served his time as a moulder, joined the Regular Army and fought in France, where he sustained a shrapnel wound of the right lower thorax, and states that his right eye was injured and had to be removed in 1919. He married after this, but had no children. He claims that marital relations were satisfactory up to 1949, although this seems doubtful.

About 1930 his voice started to get hoarse in the mornings and gradually became very highly-pitched. He also started to have difficulty in swallowing and maintains that about 1940 his hair became white and then fell out. About this time he noticed lack of strength in his fingers, which became painful at the joints. The arthritis progressed and he developed difficulty in walking. The muscles around the joints became wasted and the hands and feet deformed. Cataract was removed from his remaining eye in 1940.

In 1949 he was admitted to another hospital with a complaint of baldness, arthritis in the arms and legs and a high-pitched voice. He had a right lumbar sympathectomy, and at this time a gangrenous fourth toe on the right side, other toes seem to have been amputated a long time previously.

He was thoroughly investigated with the provisional diagnosis of "hypopituitarism and scleroderma." He was aged then 55 years. He was totally bald, with absent eyebrows and scanty eyelashes. He shaved once weekly. Pubic hair was present in the female distribution, but the axillary hair was scanty. He spoke in a flute-like husky voice. He was very thin around the face, the neck and the limbs, calves being wasted, and there was a small hæmangioma on the outer side of the right eye. Eyeballs were shrunken and the genitalia small in size. The abdomen was protuberant and the body larger in proportion than the limbs. His hands showed deformities at the metacarpal phalangeal and interphalangeal joints with marked ulnar deviation. His elbow joints were even then fixed at 120° of flexion. The ankle joints showed very little mobility and two toes were absent on the right foot and one on the left. His skin was noted to be tightly bound to the subcutaneous tissues over the feet and legs and the elbows. A patch of "scleroderma" was stated to be present over the right elbow and over both feet spreading to the lower  $\frac{1}{3}$  of the legs. There was an ulcer over the lateral malleolus which took a considerable time to heal.

He had been in hospitals on several occasions afterwards with similar complaints.

## EXAMINATION.

There did not appear to have much change from the reports of 1949 onwards. He presented a remarkable appearance (Figs. 1, 2, and 3). He was small in stature with shrunken eyesockets and completely bald, with a beak-like nose. His voice was high-pitched and husky. The elbow joints were fixed, and the hands showed gross ulnar deviation. The feet showed several toes had been removed and movement was very small. Pubic hair was scanty. There was no axillary hair and the testicles and penis were very tiny. The skin was tightly bound down to both the hands and the feet, and owing to his deformities he had not worked since 1944. The subcutaneous tissues were almost absent in the limbs and there were trophic ulcers of the feet, the right shin, and the left knee. The abdomen was protuberant and the skin over the chest more supple than on the limbs. He showed a low blood pressure with a systolic of 100 and a diastolic was not obtained. It

was noted that his pressure in 1949 had been 150/80. In all, he showed signs of marked senility except for the trunk and abdomen, and gave the impression of a plucked bird.

#### INVESTIGATIONS.

He had been fairly extensively investigated over the years and the results of these are combined for the sake of brevity.

Urinary Gonadotrophins = 4 M.U./24 hours.

Urinary 17-Ketosteroids (24-hour excretion) 2.7 mgs., 5.4 mgs. (and 6.7 mgs. in 1949).

Both these levels are on the low side, particularly the latter, and suggest some pituitary hypofunction.

Insulin sensitivity test showed marked sensitivity with levels of 72, 40, 40, 40, 40, 45, 51, 108, and 105 mgs. per cent.

Glucose tolerance test = Low-normal.

B.M.R. = Plus 4 per cent.

Radioactive Iodine test = Uptake index normal—T = 10.4.

Blood cholesterol = 100 mgs. per cent. (This had been 160 mgs. per cent. in 1949.)

Liver function tests = Serum Proteins—6 gms. per cent.

Albumin 3.6.

Globulin 2.4.

This showed a slight reduction in the albumin which was confirmed on electrophoresis. Previous level in 1949 had been normal.

Thymol Turbidity = 1.

Alkaline Phosphatase = 19.3 K.A. units.

Serum Calcium = 10.1 mgs. per cent. (Same level in 1949.)

Blood urea = 36 mgs. per cent. and 42 mgs. per cent.

Serum Electrolytes showed no abnormality in the sodium, potassium, chlorides or alkali reserve.

E.C.G. = Low voltage. F.T.M. = Normal. Wassermann = Negative.

B.S.R. = 3 mms, in one hour.

Radiological Examinations.

Skull—Shallow sella turcica.

Both feet—Marked osteoporosis with deformities of the arthritic type and calcinosis circumscripta. Several toes had been amputated.

Pelvis-Some circular areas of rarefaction.

Both hands-Marked osteoporosis and ulnar deformity (Fig. 4).

Barium swallow—There was some degree of pharyngeal dysphagia in that the pharyngeal musculature did not contract and a considerable amount of contrast remained behind trapped in the pyriform fossæ.

Legs—Marked calcification of the right tendon Achilles.

Laryngoscopy—Generalised atrophis changes in the larynx and epiglottis. The cords were pale and did not meet properly owing to lack of tone in the tensors. In places they were injected.

Skin Biopsy (Dr. J. E. Morison)—The skin shows atrophy of the epidermis.

There is some flattening of the papillæ. No skin appendages are present. The distribution of melanin is patchy and the amount varies from area to area. There is no inflammatory infiltrate around blood vessels. The pattern of the elastin in the deeper dermis is preserved, but in the immediately sub-epidermal zone it is atrophic. The appearances are entirely those of gross atrophy and are consistent with progeria and with Werner's syndrome as suggested.

### DISCUSSION.

Once the condition is recognised it is probable that many other patients will be studied and reported on, and important clues may be found to the problems of senescence and the waning of intimate cellular metabolism with age. It is for this reason worth considering the syndrome in some detail.

Heredity has been considered to be of great importance, although a familial tendency has not been found in every case (Williams, 1949; Irwin and Ward, 1953; Pomeranz, 1948). Carleton (1943) thought that the condition was heterozygous with a strong suggestion that other genes play a part in determining the expression of the major gene. The relationship to Rothmund's syndrome, a hereditary recessive disorder with cataracts, atrophy of the skin and telangiectasia in early childhood, is certainly close. Tannhauser (1945) has exhaustively gone into this subject. He drew attention to the close relationship with dystrophia myotonica, another familial disorder. Here there is the same age on onset, with cataracts and sexual underdevelopment; but attention is focused on the typical myopathy and the skin changes are not of importance.

The syndrome is, without doubt, distinctive. Although certain variations are found, the senile appearance, the cataracts, the typical habitus and facial appearance with the skin changes are universal. Its basic cause is still uncertain. Oppenheimer and Kugel (1941), who reported the first cases in America, discuss the first autopsy. A primary cancer of the liver was the immediate cause of death, a condition rare enough in itself. The syndrome itself they considered an ectodermal abiotrophy. Atrophy of the testes and prostate, hyperactive thyroid adenomata and parathyroid glands were present with metastatic calcification and osteoporosis, while the pituitary was noted to be normal. Their second case died later from a fibrosarcoma of the radius; another rare tumour. Ectodermal abiotrophy is not enough to explain such a disorder. In hereditary ectodermal dysplasia the condition starts in infancy with atrophy of the skin, baldness, and hyperkeratosis of the palms and soles, but no other disability. Atkins (1954) reports on the post mortem of a case of progeria (Hutchinson-Gilford syndrome). This is another closely related disorder—the child is born normal, there is no obvious hereditary factor, yet within a few years it stops growing and presents an appearance of premature senility. There is a similar facies to Werner's syndrome, loss of hair and fat, arthritic deformities and, in some cases, skin atrophy. Death is usually in adolescence from the results of arteriosclerosis. In the case reported the author could find nothing to support the view that the condition was due to pituitary or pluriglandular deficiency. He found only a slight loss of eosinophils in the pituitary and came to the conclusion there was an enzyme defect in the energy

metabolism cycle producing a mesenchymal dysplasia. It is probable that something similar happens in Werner's syndrome.

Williams (1949) found the 17-ketosteroids normal in his patient, but considered the source to be mainly adrenal, as a high proportion of dehydro-iso-androsterone suggested primary gonadal failure. Gonadal failure is a feature of Werner's syndrome, but its late onset suggests that the primary cause is a multisystem disturbance. Indeed, a woman aged 58 years, who married at 27 and had two children before the menses ceased at 40, is described by Brink and Findlay (1950). She developed grey hair at 18, cataracts at 31, and ulceration of the feet at 43, and although her sons were normal there was consanguinity in her grandparents. She also showed marked phthisis bulbi like the case discussed above, although other cases have been noted to have exophthalmos. Diabetes has been reported in eleven out of fifty-five cases reviewed by Irwin and Ward (1953). In a few cases there is a suggestion of mild hyperthyroidism, but most authors find the B.M.R. within a few points of normal, and the radioactive iodine test normal. Blood cholesterol values seem to fluctuate from as high as 280 to as low as 100 mgs. per cent. Osteoporosis and metastatic calcification is almost universal, yet a high serum calcium and evidence of increased parathyroid activity is only found in some instances. Pomeranz (1948) was able to diagnose a patient radiologically because of the extreme osteoporosis, calcification of the blood vessels and soft tissues, osteoarthritis and the dysharmony between the skeletal and dental age.

The skin changes are superficially like scleroderma, but microscopic examination shows atrophy of the epidermis and flattening of the papillæ. There is no evidence whatever of arteritis, lymphocytic infiltration or ædema, homogenisation or sclerosis of the collagen. The subcutaneous tissues are scanty and lack fat cells, while hair follicles and sweat glands are few in number. The skin is, therefore, atrophic except when exposed to pressure on the feet, insteps, and elbows where hyperkeratosis is found. These areas often break down to ulcers which may have some connection with depositions of calcium. Tannhauser (1945) was the first to point out the distinction and called the condition pseudo-scleroderma. The muscles were found to be swollen with loss of striations by Williams (1949) and in some areas were completely replaced by fibrous tissue. On the other hand they were reported as atrophic by Irwin and Ward (1953).

The high-pitched voice has also been remarked on and in some cases the vocal cords show a crazy paving appearance with white atrophic areas separated by bands of dilated vessels.

The syndrome, although showing variations depending upon the degree of atrophy of the various tissues and attempts at compensation by those less affected, presents an easily recognisable entity. It is remarkable, however, that mental defect does not appear to be a feature in spite of the involvement of the rest of the body. Some biochemical defect, as yet unrecognised, is probably at fault and, while the clinical features are unique, the histology has not been either helpful or specific.

#### COMMENT.

This patient had been considered to be a case of hypopituitarism with hypogonadism in association with scleroderma. He had been in hospitals on several occasions for treatment of his leg ulcers and had been thoroughly investigated. All who had seen him had noted that there was something more to it than just hypopituitarism, although the syndrome had not been recognised. There is evidence of some pituitary hypofunction as shown by insulin sensitivity and low gonadotrophins. Low ketosteroids and low blood pressure suggest associated adrenal and genital underaction. Urine at times had shown sugar, but no evidence of diabetes had been found. Blood cholesterol always seemed to have been on the low side and the thyroid function normal. There was no real evidence of parathyroid disfunction, although osteoporosis was present.

In this case we have not been able to obtain a family history. He has no offspring, but had been married.

Naturally he suffered from psychological disability associated with his condition and, as a witness, was not entirely reliable.

I would like to thank Dr. Cotton Kennedy and Mr. D. Neill for their great help and interest with the laboratory investigations, Dr. J. C. Meenan for the photographs, and Dr. J. E. Morison for reporting on the skin biopsy. I am also grateful to Dr. G. Scarlett.

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# Volvulus of the Cæcum

# And other possible results of Hypermobile Right Colon

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No one can now seriously consider hypermobility of the right colon responsible for the host of maladies—including colitis, cholecystitis and even mental changes and chronic mastitis—which were once attributed to it, nor believe, as once was claimed, that colopexy could lead to a cure of such conditions.

In rightly rejecting such extravagant claims, the pendulum of opinion has possibly swung too far, leading almost to disbelief in the condition, and to abandonment of the operation. The modern view is expressed by Gardner (1950), who writes:—"Failure of fusion of the cæcum and ascending colon and its mesentery to the peritoneum of the right iliac fossa in a normal manner allows undue mobility of the cæcum and ascending colon. This was formerly in itself thought to be the cause of symptoms, and numerous operations were devised for its correction. At present a mobile cæcum is thought to be of significance only because it may be the seat of volvulus of the cæcum, or because it may allow the appendix to occupy a position almost any place in the abdomen." This modern concept, which will admit only well-defined and tangible abnormalities as the results of cæcal non-fixation, should surely include intussusception.

Others, including Lyall (1946) and Gardiner (1947) feel that while early claims were excessive, the modern scepticism is just as far from the truth, but in the opposite direction. However, Gardiner "is hesitant to advocate a return to the days of pexis."

Support for this moderate or middle-course view is supplied by the following two cases:—

Case 1.—A man, aged 40, was admitted with a history of having been troubled, over the past twelve years, by a "steady" (not colicky) pain, situated high in the epigastrium which came on 1 to 1½ hours after food. He often obtained ease by taking baking-soda or other antacids. His appetite was poor, and he avoided certain articles of diet, particularly potatoes, that seemed specially liable to bring on the pain. This pain had occurred at intervals from its inception twelve years previously up to the day before admission. At 6 p.m. on the day before admission he had an attack of a different crampy pain and, since it did not disappear, sought relief by taking salts. Following this, the pain became much worse, and the salts failed to produce a bowel action. The pain persisted all night, but ceased spontaneously the next morning at 8 o'clock only to recur, more violently than ever, at 2 p.m. He consulted his doctor later in the afternoon and was admitted to hospital at 6 p.m.

It was only after operation that further questioning revealed that, besides the habitual long-standing epigastric pain, he had, on occasions over the years, experienced attacks of pain of a different character. These attacks had occurred only once or twice

a year, and consisted of colicky mid-abdominal cramps. The attacks lasted about an hour and, characteristically, ended with a relaxed bowel motion. The attack of pain preceding admission was of this type, and it was in expectation of the customary relief that he had tried to obtain a bowel action by taking salts.

On examination there was muscular guarding in the whole abdomen, and tenderness and rebound tenderness were evident in all areas, though maximal in the region of McBurney's point. Distension, though present, was not a conspicuous feature. Some abdominal catastrophe had evidently occurred, and in view of the long history of epigastric pain occurring after meals and relieved by alkalis, it was thought most likely that he had a perforated ulcer. Perforated appendicitis was also considered. The stomach was aspirated, and an intravenous drip saline infusion started. A plain X-ray (erect) of the abdomen was taken, with the expectation that this would probably show free sub-diaphragmatic gas, thus confirming the diagnosis of perforation. Instead, the film revealed a large gas-shadow under the left diaphragm, with a semi-circular upper border and a straight horizontal base. In size, shape, and position this resembled the air-bubble of the gastric fundus, but the tip of the Ryle's tube did not lie within this shadow. This observation was puzzling, but its significance was not appreciated at the time.

At operation an enormously dilated portion of bowel, almost filling the left upper quadrant of the abdomen, was felt, and, after enlarging the wound to make delivery of it possible, this was found to be the cæcum. This had undergone anti-clockwise torsion through 360 degrees and had subsequently enlarged and migrated upwards and to the left. The neck of the volvulus was the point at which the terminal ileum was twisted round the lower ascending colon. The volvulus was untwisted and, after a few adhesions at its neck had been divided, some of the fluid and gas it contained could be milked onwards in the colon. The gut appeared viable, but on account of the tremendous stretching and thinness of its wall, it was thought unwise to suture it to the right iliac fossa; the cæcum was merely replaced in this position, and, to facilitate closure of the abdomen, a large quantity of the fluid and gaseous cæcal contents was aspirated through a wide-bore needle.

On the fourth day the bowels were opened and a large quantity of flatus expelled.

Fixation of the cæcum was carried out on the fourteenth day. When the abdomen was reopened the cæcum was found to have remained in the right iliac fossa. It was much smaller than formerly, though still considerably distended. The appendix was removed. A flap of peritoneum was elevated over the iliacus muscle, the cæcum placed in the raw area exposed, and the flap turned down and sutured to the anterior tænia.

The patient was discharged two weeks later, feeling very well. He was seen subsequently on several occasions.

In view of the twelve-year history of hunger pain, relieved by food and alkalis, a barium meal was carried out two months after discharge. This showed no evidence of duodenal ulcer, and the progress of the meal was normal. A barium enema a short time later showed the cæcum to be of normal calibre and lying in the right iliac fossa; there was some slight convolution of the ascending colon, but otherwise no abnormality was seen.

When seen eight months after operation he stated that he "had never felt better." He had no pain of any kind, had a much-improved appetite, could eat anything (including potatoes) with impunity, had put on weight, and had resumed farm work.

#### Discussion.

Several points of interest appear in this case. Most reported cases seem to have presented as typical intestinal obstruction, and marked distension is usually a feature. The absence of marked distension, and signs of acute obstruction in

the present case, though unusual, is not unique. Stillman (1948) mentions that the attack may not be typical of acute intestinal obstruction, and Gardiner states that "distension may be late in manifesting itself." It is felt that the absence of gross clinical distension in the present case was due to the cæcum lying largely up under the left costal margin. With regard to this position of the cæcum it is interesting to note that Gardiner remarks that (on X-ray) the greatly dilated cæcum may be mistaken for dilated stomach, and other writers have pointed out that cæcal volvulus not uncommonly occupies the left hypochondrium: Weinstein (1938) calls this "Type 2," and Wolfer (1942) quotes Corner and Sargent as stating that the left hypochondrium is the most common site of clinical cæcal volvulus. Rothman (1943) and McGraw (1948) state that the appearances on straight X-ray are sufficiently characteristic to enable a correct pre-operative diagnosis to be made in most cases. Other writers feel that barium meal or barium enema should be done in suspected cases and have described the findings obtained, but such investigations in an acutely ill patient are surely unwarranted—even if the diagnosis cannot be made from a straight X-ray the clinical features are such as to demand immediate operation; further investigations can only lead to delay, the dangers of which are obvious enough. Moreover, barium enema has been recorded as actually having precipitated an imminent cæcal volvulus (Jungmann, 1948).

The objects of the two operations in this case were (1) to deal with an acute abdominal emergency and (2) to minimise the likelihood of a recurrence. The patient was relieved of the attacks of incomplete large bowel obstruction from which he had previously suffered. He was also relieved of a dyspepsia which had for long mimicked a duodenal ulcer. This was unexpected and most gratifying, and is perhaps the most interesting aspect of the case. That a chronic twelve-year dyspepsia is dramatically relieved following an operation does not, in a single case, prove that the operation was the cause of the relief, but it is suggestive.

The following case, encountered shortly afterwards, makes it more suggestive still:—

Case 2.—A labourer, aged 54, had complained for four years of epigastric burning pain before meals, relieved by food for 1 to  $1\frac{1}{2}$  hours. There were periods of remission of from six to eight weeks. He stated that the pain had on occasion wakened him at night. At first the pain had been relieved by "white powder," but this had recently ceased to be effective. There was epigastric tenderness. A barium meal in 1950 had shown changes suggestive but not conclusive of duodenal ulcer. A further barium meal in 1952 did not show any evidence of ulcer. Exploratory laparotomy was carried out because of persistent symptoms. No evidence of peptic ulcer was found, and the only significant abnormality was a very excessively mobile cæcum and ascending colon. Fixation was carried out in exactly the same way as in the first case. When the patient was seen nine months later he stated that he had never experienced the epigastric pain since the operation.

These two cases suggest that abnormal mobility of the right colon, as well as permitting understandable mechanical complications, may lead to less well-defined conditions, difficult of explanation to the surgeon, but no less distressing to the patient. They further suggest that surgical fixation of the abnormally mobile gut may relieve these symptoms.

This belief has been stated by Coffee (quoted by Donhauser and Atwell, 1949): "I am convinced that over one-half of the patients complaining of right-sided pain have no definite organic disease, but have defective fixation of the ascending colon." Carslaw (1928) described 32 cases of right-sided visceroptosis giving rise to symptoms like those of duodenal ulcer, and the same author quoted Waugh's series of 518 cases, of whom 97 had hunger pain, but none had duodenal ulcer. The probable mechanism of production of these symptoms has been fully discussed by these writers.

Ptosis of the cæcum is a very common condition: Bryant (1921) gives the incidence as 12.1 per cent. of males and 39.4 per cent. of females, and Miller (1940) quotes similar figures. The majority of these give rise to no symptoms, and it would be absurd to suggest that colopexy should be performed in all. Is there not a happy medium between, on the one hand, wholesale anchoring of all mobile cæca, and, on the other, completely disregarding the existence of this condition? There would seem to be a case for carrying out fixation in those cases where no other abnormality is found to account for dyspeptic symptoms.

#### SUMMARY.

- 1. A case of volvulus of the cæcum is described where fixation of the hypermobile gut relieved not only the obstructive symptoms but also a long-standing epigastric pain simulating peptic ulcer.
- 2. While volvulus is perhaps the most dramatic, it is probably not the most common disturbance that can result from hypermobility of the right colon, and other ill-effects merit more consideration than they receive.
- 3. Visceroptosis is no longer a reputable ailment nor colopexy a fashionable operation. On the other hand, puzzling cases are still encountered in which no abnormality other than cæcal ptosis can be found to account for dyspeptic symptoms. It is suggested that it would be worthwhile carrying out fixation in these cases and making a further study of the results.

I wish to thank Mr. C. S. Wilson for permission to publish the cases described in this article, and Professor H. W. Rodgers for helpful criticism and advice.

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# Renal Lesions in Choline Deficiency in Rats

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During the course of experiments with rats fed on a vitamin A deficient diet deaths occurred from a hæmorrhagic degeneration of the kidneys. The changes found in the kidneys resembled those described in choline deficiency by Griffith and Wade (1939). In their experiments the hæmorrhagic renal lesion was always accompanied by marked fatty degeneration of the liver, while in our experiments the liver lesions were often minimal. Hartroft (1955) has recently reported fat embolization of the renal arterioles and capillaries in chronic choline deficiency and has supported the view that the fat is derived from the liver. The same author (1947 and 1948) described fatty infiltration of the proximal convoluted tubules in acute choline deficiency.

In our rats the relative absence of fatty change in the liver did not correspond with the accepted description of choline deficiency. Further experiments were carried out to determine if the renal changes were a manifestation of choline deficiency, and if there was any evidence of fat embolization in the kidney.

# MATERIALS AND METHODS.

The original observation was made by one of the authors (M. G. McG.) during an experiment in which a group of 100 Wistar albino weanling rats was fed on a vitamin A deficient diet for the purpose of producing renal calculi (Higgins, 1933, 1935). The diet used was similar to Higgins' diet and was composed as follows:—

per cent.

Caseinum soluble (B.P.C.).	-	-	-	-	18
Dextrin	-	-	-	-	65
Arachus oil	-	-	-	-	10
Dried brewer's yeast* -	-	-	-	-	2
Salt mixture†	_	-	_	-	5

<sup>\*</sup>Aluzyme, containing aneurin, nicotinic acid, riboflavine, pyridoxin, pantothenic acid and folic acid.

Higgins did not report any deaths from choline deficiency kidney in his rats fed on this diet.

In the experiment in which the original observation was made 30 male rats died in a batch of 50, while only 4 of a batch of 50 females died (Experiment I in Table 1). Five further experiments were carried out, using 170 rats. In Experiment II rats aged 5 to 6 weeks were used and all the animals survived until they were killed after three weeks on the diet. The kidneys were found to be normal in all these rats. In the later four experiments weanling rats (aged 26 days) were

<sup>†</sup>NaC1, MgSO<sub>4</sub>, NaH<sub>2</sub>PO<sub>4</sub>, KH<sub>2</sub>PO<sub>4</sub>, CaHPO<sub>4</sub>, Fe citrate, Ca lactate.

used, and in all of these experiments renal lesions were found in some of the animals. In Experiments II, III, and IV some of the rats were given supplements of choline chloride in their drinking-water, at the level of 35 mg. per rat per day in Experiment II, and 6 mg. per rat per day in Experiments III and IV and V. After it had been established that choline chloride completely prevented the lesions in the kidneys, Experiments V and VI were carried out to obtain material representative of the very early lesions and of the healing stage.

Post-mortem examination was carried out in all the animals except for a few which died during the night and were eaten by their litter mates. The animals which died and were eaten are presumed in Table 1 to have died from the renal condition as all deaths in the animals subjected to post-mortem examination were due to renal damage. The majority of the rats were killed by inhalation of ether in a closed chamber, a few being taken from each group from the ninth or tenth day onwards. All surviving rats were killed after three weeks. In Experiment VI animals were killed from the sixth day onwards. As a routine, blocks for histological examination were taken from the lobes of the liver and from the kidneys. In addition, in a small number of rats, blocks were taken from the lungs, heart, spleen, small and large intestine, skeletal muscle, brain, and spinal cord. The blocks were fixed in Helly's fixative, and in many rats duplicate blocks were fixed in 3 per cent. formaldehyde (7.5 per cent. formalin) for preparation of frozen sections for fat stains. Sections were stained with hæmotoxylin and eosin, and with Scharlach R for fat.

In some of the rats, bacteriological examination of the kidneys, spleen, and blood were carried out, but no organisms were seen in smears or grown in cultures.

#### RESULTS.

On the fifth day on the diet affected rats began to appear thin. Deaths occurred from the seventh to the twelfth day. In all the experiments some of the rats appeared to escape, while animals in the same cage died. In the experiments in which rats were allowed to survive for three weeks some of the affected animals appeared to recover, although the diet was not changed and no choline was given. At post-mortem healing lesions were discovered in some rats which had not appeared to be ill. A summary of the experiments is given in Table 1.

Experiment I is the experiment in which the lesion of the kidney was first observed. None of these rats received supplements of choline. In Experiment II rats aged 5 to 6 weeks were used. Some of the rats were given choline, but neither these nor the rats which did not receive choline developed renal lesions. In Experiment III 26-day-old rats were used, some being given a supplement of choline. In this experiment renal degeneration occurred amongst the rats without the choline supplement, but not amongst those given choline. The absence of hæmorrhagic kidneys in Experiment II was thought to be due to a decreased susceptibility to choline deficiency in older rats. Griffith (1940) reported that there was a marked decrease in the incidence of renal lesions due to choline deficiency in rats aged 33 days and older. The rats used in Experiments IV, V, and VI were all aged 26 days. In Experiment IV choline was given to some of the rats and no

renal lesions occurred amongst these rats, although they were frequently present amongst those not given choline. The results of Experiments III and IV and V were taken as evidence that the renal lesion to be described later was a manifestation of choline deficiency.

# Pathological Changes in the Kidney.

In the animals which died or appeared to be acutely ill the kidneys were found to be greatly enlarged, often to twice or three times the size of the kidneys of unaffected rats. The cortex was dark purple-red, contrasting with the grayish-red

TABLE 1.

Experiment		WITHOUT ADDED CHOLINE								WITH ADDED CHOLINE							
		No.		No.						No.		No.					
		Male	F	ema	le	RENAI	. Le	SION	s	Male	F	'emal	le	RENA	ı. I	LESIONS	
						No.		No.						No.		No.	
						Male	F	emal	e					Male	. ]	Female	
Ι	Weanling	. 50		50		30		4		0		0		0		0	
						(60%)											
II	5-6 weeks	. 10		10		0		0		6		0		0		0	
Ш	26 days	. 7		6		3		1		4		3		0		0	
					(	(43%)	) (	17%	5)								
IV	Weanling	. 13		12		9		6		12		13		0		0	
					(	(69%	) (	50%	5)								
V	Weanling	. 8		10		1		7	• • • •	10	• • •	10		0		0	
					(	(12%)	) (	70%	5)								
VI	Weanling	. 25	• • •	0				0	•••	0	•••	0		0		0	
					(	(56%)	)										

of the medulla. The increase in size was due to swelling of the cortex. In animals which survived for twelve days or longer the kidneys were still enlarged, but less dark in colour. Later the cortex became yellowish brown in colour, with small purple-red patches here and there. These kidneys were larger than normal, but a considerable decrease in size had occurred when compared with kidneys of rats which had died in the acute stage. In a few of the animals surviving for three weeks the kidneys were found to be normal in size or slightly smaller than normal. The cortex was covered with dense white specks, which on the cut surface could be seen as streaks extending towards the cortico-medullary junction.

# Microscopic Appearances.

The earliest lesion was the appearance of fine granules of stainable fat in the cells of the proximal convoluted tubules. This was already present at six days. A little later the fat granules were apparent in the loops of Henle and in the distal convoluted tubules. In the less severely affected cells the fat was situated at the base of the cells. The fat was present in kidneys in which the tubule cells appeared only slightly swollen when stained with hæmatoxylin and eosin. In the fully developed lesion the nuclei of many of the tubules had become pyknotic or had

disappeared and the cells had been replaced by amorphous eosinophilic debris. In some kidneys the necrosis involved the complete periphery of the cortex, but in others only small areas were affected. In the most severely affected kidneys the glomeruli were necrotic, but frequently these had escaped while their tubules were packed with fat or were necrotic. In some of the kidneys there was extreme congestion of the cortex, and hæmorrhage was present under the capsule, together with a little fibrin. Many of the tubules contained large eosinophilic casts which were most numerous in the region of the cortico-medullary junction. When stained for fat these casts contained little or no fat. The glomeruli were usually free from fat except when they had become necrotic, and there was seldom stainable fat in the blood vessels. The vascular system was normal except in areas where complete necrosis of the cortex had occurred.

In the healing stage proliferating fibroblasts appeared and calcium was deposited in necrotic tubule cells. Some of the casts also became calcified. A few mononuclear cells were sometimes present but infiltration with inflammatory cells was never marked. The necrotic cells gradually disappeared and in the oldest lesions there remained a wedge-shaped scar of fibrous tissue containing the calcified remains of a few tubules.

# Pathological Changes in the Liver.

In the majority of the affected rats the liver appeared normal in colour, consistency, and size on naked-eye examination. In occasional rats it was slightly pale, but it was never enlarged. It was difficult to detect any macroscopic difference between the livers of the rats which had renal lesions and those in which the kidneys were necrotic. The livers were normal in the rats which had received choline.

# Microscopic Appearances.

Microscopically the livers of most of the rats contained a little fat, whether they had received choline or not, but in many it was periportal in distribution. In rats without choline supplements to the diet sometimes the liver contained small amounts of centrilobular fat. The amount of this did not correspond to the presence or the severity of the renal lesions, some of the rats with histologically normal kidneys having considerably more fat than others in which the cortex was almost completely necrotic. The small amount of fat present in the livers of many rats with renal necrosis could not be explained by the rapid disappearance of liver fat during early healing, as it has been noted by Griffith (1941) and Christensen (1942) that the fatty infiltration of the liver remains during the recovery phase of the disease.

The fat in the livers and kidneys was not doubly refractile.

No abnormalities were detected in the lung, heart, spleen, intestine, skeletal muscle, brain or spinal cord in those rats in which they were examined.

#### DISCUSSION.

The fully developed lesion in the kidneys of these rats bears a close resemblance to the choline deficiency kidney first described by Griffith and Wade (1939), and

also reported by Christensen (1942), Wachstein (1944), Baxter (1947), and Hartroft and Best (1947). It resembles Griffith's hæmorrhagic degeneration of the kidneys in that it can be prevented by choline. However, in Griffith's rats the liver showed marked fatty degeneration, and both he and other workers have reported that amounts of choline sufficient to prevent renal necrosis do not protect the liver, the liver being apparently more sensitive to choline deficiency than is the kidney. It was interesting that in the experiments described here the rats with the most severely affected kidneys often had relatively little fat in the liver, while some animals with fatty livers had normal kidneys. While the majority of reports of choline deficiency kidneys state that the liver was very fatty, Baxter (1947) reported that "most of his rats with hæmorrhagic kidneys had slightly to markedly fatty livers."

In these experiments the glomeruli were often undamaged when the tubules beneath the renal capsule had become necrotic, and only when extensive areas of the cortex had become necrotic were they involved. The primary lesion in choline deficiency kidney appears to be damage to the tubules. Dessau and Oleson (1947) also report that the glomeruli tend to escape in acute choline deficiency. However, the renal lesions in chronic choline deficiency involve the glomeruli (Hartroft, 1955), and the histological appearance is quite different from that of acute choline deficiency.

Griffith (1941) observed abundant fat droplets in the bases of the necrotic cells. Hartroft and Best (1947) reported the early appearance of fat droplets in the proximal convoluted tubules, increasing in size and number until congestion, hæmorrhage, and necrosis occurred. Hartroft (1948) suggested that the necrosis might be due to compression of the cortical capillary plexus by the swollen fat-filled cells of the proximal convoluted tubules which he called tubular obstruction of capillaries. In the experiments reported here congestion was not invariably a marked feature of the necrotic kidneys, although it occurred in many of them. This suggests that tubular obstruction of capillaries is unlikely to be the cause of the necrosis. Dessau and Oleson (1947) also favoured interference with the vascular outflow of the kidney as the cause of necrosis in choline deficiency.

The source of the fat in the cells of the renal tubules is not often considered. It would seem unlikely to have been carried to the cells in the blood stream, as the glomeruli are usually free of fat while the cells lining their tubules are full of it. The fact that the degree of fatty degeneration of the liver often does not parallel the renal changes would also tend to exclude the possibility of the renal fat arriving via the blood stream. It is possible that fat from the blood stream could have been filtered through damaged glomeruli and then have been reabsorbed by the tubules. However, the fat lies near the basement membrane of the tubules instead of near the lumen, as it would be expected to do if it had been absorbed from the glomerular filtrate. The casts, which are numerous, are not composed of fat, as they would have been if fat had escaped through damaged glomeruli. The most likely explanation of the fat in the renal tubules would appear to be a direct result of choline deficiency on the tubule cells, causing a phanerosis of fat already present in non-stainable form.

The diet used in these experiments was low in vitamin A content as well as in choline, but it was not completely absent from the casein preparation used. Other batches of animals on the same diet did not develop signs of vitamin A deficiency until after several months. The renal changes occurred within seven to twelve days, and it is unlikely that these were related to or modified by vitamin A deficiency.

#### SUMMARY.

Degenerative lesions in the kidneys of rats fed on a vitamin A deficient, choline deficient diet are described. The earliest change was a fatty infiltration of the renal tubule cells, which progressed to necrosis. Glomerular involvement was often minimal and appeared to be secondary to tubular damage. There was no evidence that it was of vascular origin, and it would appear to be due to specific effect of choline deficiency on the tubular cells. Fatty infiltration of the liver occurred in some of the rats, but it frequently did not correspond in severity to the degree of renal damage.

We wish to thank Professor J. Henry Biggart for his advice in carrying out this work. Mr. J. Davidson kindly prepared the sections.

M. G. McGeown wishes to acknowledge the receipt of a grant from the Medical Research Council.

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# **REVIEW**

A TEXT-BOOK OF MENTAL DEFICIENCY. By R. F. Tredgold, M.D., D.P.M., and K. Soddy, M.D., D.P.H. Ninth Edition. (Pp. xv + 480; plates 31. 40s.) London, Baillière, Tindall & Cox, 1956.

This text-book was first compiled by the late A. F. Tredgold and for many years was a standard text-book and one of the classics of the subject. The present work is in great part rewritten, but the late author's case histories and descriptions have been retained and give an interesting early century atmosphere to a book where the conflicting theories of modern psychology are presented and related to other aspects of mental deficiency. The practical and legal aspects of the problem also receive a balanced presentation.

The diet used in these experiments was low in vitamin A content as well as in choline, but it was not completely absent from the casein preparation used. Other batches of animals on the same diet did not develop signs of vitamin A deficiency until after several months. The renal changes occurred within seven to twelve days, and it is unlikely that these were related to or modified by vitamin A deficiency.

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### Whitla's Dictionary of Treatment

1892 - 1957

One thousand nine hundred and fifty-seven began auspiciously for the Belfast Medical School with the appearance of the ninth edition of Whitla's "Dictionary of Medical Treatment." The first edition appeared in January, 1892, and was one of the outstanding medical text-books of its time. William Whitla was 42 years of age, had held the Chair of Materia Medica for about a year, and his text-book on Pharmacy, Materia Medica and Therapeutics had already met with great success. There were "suggestions from many members of the profession, both teachers and practitioners, upon the necessity of appending to it a Therapeutic Indix or Index of Diseases." Many years later he told Dr. Allison that he had written some hundreds of pages of manuscript of the new text-book, but became so busy in his practice that he put these pages aside for some months. When he looked at them again he thought so badly of them that he instructed his manservant to take them and have them burnt in the furnace of a factory not far from his house. By a happy chance, the factory was closed that particular day, and the manservant put the papers on a shelf, where they remained for some time. Again Whitla read them, this time with more pride in them, and resumed his labours. The circumstances of the publication of the Dictionary were possibly unique. It seems to be beyond doubt that Whitla took his manuscript to London, and when the publisher, Henry Renshaw, seemed a little hesitant to accept it, the author explained that he did not intend that Mr. Renshaw should publish it in the ordinary way, but that he, Whitla, would see to the printing, publishing, and distribution, and would allow the nominal publisher a small percentage of the profits in return for the use of his name on the flyleaf. He is reported to have said: "I cannot have the book appearing, written by William Whitla, printed by William Whitla, published by William Whitla: all I require from you is your name on the flyleaf, and I am willing to pay you for it. You cannot lose anything." This arrangement proved a most lucrative one for Dr. Whitla, and may well have been the foundation of his fortune. His acumen in financial matters became the constant cause of the admiration, indeed the envy, of his stockbroker.

His appearance was impressive, even awe-inspiring, but one soon found that he was essentially a simple, kindly man, with a saving sense of humour. His personal qualities, his skill as a physician, and the quality of his authorship did much to establish the reputation of the Belfast Medical School, the foundation of which had been so securely laid by such men as James McDonnell, Henry MacCormac, Thomas Andrews, Peter Redfern, and Alexander Gordon. It is not surprising that this man, who had begun life as a pharmacist's apprentice, and whose undergraduate career had already rewarded him with a gold medal in his M.D. examination, should have achieved the distinction of knighthood, honorary degrees from four universities, and the pro-chancellorship of his own. It is not

only because of his own magnificent gifts and bequests that he is remembered here, and his name is not forgotten in distant lands. It is scarcely surprising that when Professor Macafee was in Shabani in Southern Rhodesia some months ago he was reminded of Sir William's wide fame when he met a pharmacist who has owned the first to eighth editions, and who was thrilled to meet someone "who had shaken hands with Whitla." (It is almost unnecessary to add that Professor Macafee has sent him a copy of the ninth edition.)

The first edition was dedicated "To Professor Gairdner, M.D., LL.D., in recognition of his eminence as a physician, clinical teacher, and scientific observer, of his culture and erudition, of his goodness of heart and nobility of character."

In 1892 Whitla was Extern Examiner in Materia Medica and Therapeutics in the University of Glasgow, where Gairdner was the Professor of Medicine from 1862 until 1900. He was one of the greatest clinical teachers in Scotland, and became K.C.B. and F.R.S. Throughout his long life he maintained his friendship with William Whitla, and during his last illness he wrote to ask him "If there is not among the crowd of new or old cardiac remedies known to him one which could be trusted simply to advance the rate of pulsation without in any way exerting any toxic or deleterious influence when used continuously." After a series of Stokes-Adams attacks he died in 1907. Sir William's copy of the biography written by G. A. Gibson is inscribed on the flyleaf, "In sweet memory of my revered friend." The book "supplied a long-felt want," for Whitla was one of the pioneers of this index method, which made for easy consultation by a busy practitioner." "The Lancet" published a long and commendatory review: "It may at once be said that Doctor Whitla has very fairly succeeded in what might almost have been thought a superhuman task in supplying a book which is intended to serve as a guide to the practical treatment of almost everything that is capable of being treated by drugs . . . as usual, his list is longest where the results are most doubtful and unsatisfactory, e.g., five pages are devoted to asthma, and no fewer than eight diets for diabetes are given in full." In this respect we must remember that in 1892 adrenalin and ephedrine had not dawned on the medical horizon, and that the eight diets quoted for the treatment of diabetes were each associated with the name of some expert of continental reputation. It is pathetic to note throughout almost all these schemes that while carbohydrates are reduced to the utter minimum, fats are given generously; but it is interesting to note that "the writer, in conjunction with Professor Brunton, had recently the privilege of witnessing some important experiments in the laboratory of Professor Lépine of Lyons, in support of his theory of the bipolar action of the pancreas, and there is little doubt but that a distinct advance is being made since his discovery of a glycolytic ferment in the blood." (Sir Lauder Brunton was afterwards the first Extern Examiner in Materia Medica in the Queen's University, and it was not until 1923 that Banting and Best made insulin available in this country for the treatment of diabetes.) "The Lancet" and also "The British Medical Journal" were both critical of Whitla for "an unnecessarily elaborate note on M. Pasteur's method of treating persons bitten by rabid dogs." These are but examples of the prescience which Whitla so often showed, and his

remarkable knowledge of the trend of events in medicine. It is indeed a fascinating book, this first edition. To our modern taste, the style at times seems florid, and even pompous, but in spite of this he establishes a kind of intimacy with his readers, and while he gives many choices of treatment, he almost always expresses a preference based on his own personal experience. Sometimes the drugs he names seem almost mediæval, as they are now so long forgotten. For example, in the treatment of chronic inflammation of the bladder he mentions: triticum repens; alchemilla arvensis; uva ursi; pareira brava; zea mays, but appears to pin his faith to the oral administration of boracic acid. His human sympathy lights up his pages, as when he writes under the heading of the treatment of gonorrhœa: "Smoking is said to be injurious. The writer has not, however, satisfied himself about this, and, moreover, it is the only solace left to the unhappy victim, who is often so tortured with remorse that his state of mind reacts on his disorder." There is no article on hypertension in this first edition, and indeed increase in blood pressure is scarcely mentioned, except briefly in relation to nephritis. While the first edition was in great demand in the United Kingdom, Whitla published a reprint, with certain amendments of text, in the United States. This was printed in Philadelphia, but it is said that when sales were going rather slowly there he had the remaining volumes shipped to England to satisfy the demand of the home market. Soon an unexpected development took place. Dr. David Duncan Main, a missionary of the Church Missionary Society in China, was so impressed with the Dictionary that he translated it into Chinese, and the second and third editions were both published in Hangchow. As he himself wrote: "I believe that a thorough practical acquaintance with this book is of the first importance to our native assistants and students in connection with medical mission work. It contains everything they require wthin a small compass . . . the work will fill a want, and supply in almost every case what you have a right to expect in consulting it."

Dr. Main was a Fellow of both the Royal Colleges of Edinburgh and a Mandarin of the Fifth Class in China. The Chinese called him "Doctor Apricot of Heaven Below" (here one's thoughts digress to wonder what parallel names might be chosen for the editors and contributors to the ninth edition). Main also translated into Chinese Caird and Cathcart's "Surgical Handbook" and Playfair's "Textbook of Midwifery."

In 1894 the fourth edition appeared, in the preface of which the author stated that the second and third editions had been published in the Chinese language. It was dedicated to the Reverend Thomas Hamilton, President of Queen's College, Belfast. For the first time, the author had obtained direct collaboration, rather than relying on his own vast and varied experience. It should be remembered that after his period as a Resident Medical Officer in the Royal Hospital in Frederick Street, when "he practically revolutionised the work of that institution," he was attracted to surgery, and for some years assisted Professor Alexander Gordon in all his private operations. Mr. A. B. Mitchell contributed articles on surgery, and Dr. Cecil Shaw those on diseases of the eye, ear, nose, and throat. At that time Mitchell was already operating on chronic gastric ulcer (although duodenal ulcer is nowhere mentioned in the book), and for the repair of perforated gastric

ulcers: "If operation is undertaken within twelve hours of perforation the mortality is not more than 25 per cent., delay beyond twelve hours doubles this mortality." Mr. Mitchell became one of the most successful abdominal surgeons in this country. Dr. Cecil Shaw was a leading ophthalmologist, who was on the staff of the Belfast Ophthalmic Hospital and a Lecturer in Queen's University.

The fifth edition appeared in 1912, dedicated "To British Medical Missionaries in many foreign lands. . ." It had grown to 1,200 pages, and was the first to be published by Baillière, Tindall & Cox. A new feature—and a most valuable one—was that the sections on gynæcological and obstetric treatment were from the pen of Mr. R. J. Johnstone, afterwards Professor Sir Robert Johnstone. Arterial hypertension as a clinical entity makes its first appearance with a précis of the recent work of Clifford Allbutt. Under tabes dorsalis "the writer" states that "there is still more conclusive evidence of the cause being invariably of syphilitic origin," but that "mercury and iodides are of a narrow range of usefulness, and in the advanced stage of the disease they always do harm." "606" was already on trial in the Royal Victoria Hospital. These are only two examples of "the changing vesture" of therapeutics.

The sixth edition is dated 1920, and was dedicated to Sir Richard Havelock Charles, G.C.V.O., M.D., F.R.C.S.I., in recognition of this great Queensman's distinguished services in India. (There is a portrait of him in the Students' Union.) The surgical contributors were the same, and the additional help of Mr. S. T. Irwin and Mr. Wiclif McCready was acknowledged. This edition was little less bulky than the fifth, being 1,053 pages instead of 1,200. That six pages are devoted to the management of scarlet fever indicates the importance and severity of this disease at that time, and one and a half pages are given to chlorosis, a disease now almost forgotten. In his section on disease of the optic nerve he notes that "trephining is urged by Horsley and Risien Russell in every case of cerebral pressure in which choked disc is present . . . in this way blindness may be prevented."

In 1920 Sir William retired from his Chair and his wards, and spent several happy years as the representative of the Queen's University in the House of Commons at Westminster, where he rapidly established himself as a most popular member. He had not lost his interest in therapeutics, for in 1923 he produced the seventh edition—the last to come from his own fluent pen. Again he changed the dedication, this time "To the sacred memory of the five hundred heroes trained at the Queen's Universty of Belfast who fell in the Great War, and amongst their surviving companions to perpetuate the memory of a victorious comradeship in arms consecrated by so many sacrifices and so much heroism." The format was changed to a larger page, but the thickness of the book rose again, to 1,100 pages. Mr. S. T. Irwin took over the surgical articles formerly contributed by Mr. A. B. Mitchell. It is obviously impossible to detail in a short article all the changes in the text of each succeeding edition, for this would be a history of British therapeutics for sixty years, but here one may remark that it is in this edition that disease of the coronary arteries is first mentioned as "a cause of cardiac degeneration."

It was not until five years after "the writer's" death at the ripe old age of 83 years that Dr. Sydney Allison undertook the formidable task of preparing a new, eighth, edition of this famous old book. In the work of rewriting and rearranging the text he had the invaluable help of Mr. Cecil Calvert as Surgical Author, and they enlisted ten colleagues, all of the Belfast Medical School, as special contributors. The eighth was larger than any of its predecessors, totalling 1,280 pages, and covered a vast range of subjects. Three great new weapons appear in the armamentarium, insulin in diabetes, liver in anæmia, and the sulphonamides—but there is the emergence of a new enemy, or an old one better recognised, for there are several references to cancer of the lung. A large part of this 1938 issue was destroyed by enemy action, but the authors took the opportunity of reviewing and modifying the text for the reprint which appeared in 1941.

The new, ninth, edition\* is virtually a new text-book. Dr. Allison and his new co-editor, Dr. Crozier, wisely decided to limit it to medical treatment, as the many advances on so many fronts would have made the inclusion of surgery, gynæcology, and ophthalmology require a volume so compendious as to be clumsy, or so condensed as to be "tabloid." They have enlisted twenty-six contributors, all of them members of the Belfast Medical School and most of them its graduates. Of the 273 articles, 256 are written by Queensmen. Of these, 16 qualified between the years 1935-1945—no decennium in our history has produced graduates of brighter promise than these ten years. Almost every contributor had the experience of war service abroad or afloat, and both editors served in both wars. It would be invidious to mention any individual contribution where all are good. One pleasing feature of the book is that the articles are, in the main, proportionate in length to the importance of their subject. Another is the uniformity of style of presentation, which may be due in part to editorial expertness; but another reason for this may well be the close companionship in clinical service which has been shared by so many of the authors. They have placed before us in a most acceptable form the current opinions which are being taught in Belfast. Dare it be suggested that some reflected credit is due to their teachers, who were in their turn the pupils of Whitla and Lindsay, of McKisack and McQuitty, and so many others who have created and maintained a high tradition? Whatever the reason, the twenty-eight authors have outnumbered in happy harmony Mark Twain's description of the marital felicity of Brigham Young and his twenty-three wives: "Twenty-four minds with but a single thought, twenty-four hearts that beat as one." If one may offer a criticism it is that sometimes they—the contributors—are too modest to say clearly which of several treatments they personally prefer, unlike "the writer," Sir William, who was more positive in his recommendations. A small suggestion is that in the tenth edition each contributor should place his

<sup>\*</sup>WHITLA'S DICTIONARY OF MEDICAL TREATMENT. Edited by R. S. Allison, V.R.D., M.D., F.R.C.P., D.P.M., and T. H. Crozier, M.D., B.Sc., F.R.C.P. Ninth Edition. (Pp. xiv + 854. 52s. 6d.) London: Baillière, Tindall & Cox, 1957.

initials at the end of each article: it is interesting to know whose pen it is without recourse to the list of authors in the opening pages. The book is a credit to the publishers: its binding, paper, and print are all pleasing, and its price (52s. 6d.) moderate for 854 valuable pages.

In his later years Sir William became greatly interested in the prophet Daniel. For this reason, words from the fourth verse of the first chapter of the Book of Daniel were inscribed on his memorial tablet in Ward 2 of the Royal Victoria Hospital, Belfast: "Skilful in all wisdom, cunning in knowledge and understanding science." These words had been ascribed by the prophet to certain of the children of Israel, and seemed to describe Sir William. Could he have lived to read the ninth edition, he in turn might well have applied them to his twenty-eight successors.

The Whitla Medical Institute, given by Sir William in 1902, differs in architectural style from the Sir William Whitla Hall of 1941, but such was his progressive mind that he would have loved the new architecture as much as the old. Similarly, he would have loved the new book, which fittingly honours his memory, perhaps most of all because it differs from his first edition—then an innovation—written sixty-five years ago.

It is a very real pleasure to commend this book, which is an achievement worthy of Sir William Whitla's great name and of the place he served so well.

ROBERT MARSHALL.

### Spontaneous Hæmopneumothorax

By C. F. Brennan, M.B., M.R.C.P.I.; and Evan Fletcher, M.D., M.R.C.P.

The Belfast City Hospital

Massive hæmorrhage is a rare complication of spontaneous pneumothorax (Agnew, 1955). The pneumothorax often arises as the result of rupture of a subpleural cyst or bleb (Coope, 1945). It is presumed that, with the collapse of the lung, pleural adhesions are torn. It is from the torn parietal ends of these adhesions, which are uninfluenced by the collapsed lung, that bleeding may arise (Hartzell, 1942). The condition is very often serious and carries a mortality rate of between 15 and 25 per cent. (Calvert and Smith, 1955; Ross, 1952).

The following case exhibits some of the features of this condition.

#### CASE REPORT.

A 22-year-old male fitter was admitted to hospital on the 20th November, 1956. Two days prior to this day he was seized with a severe pain in the left chest and, at the same time, experienced a sensation as if water was running down his back. He remained at work, but eventually had to stop because of breathlessness on exertion and a feeling of faintness. The other significant symptoms were those of flatulence and vague epigastric pain over the preceding twelve months.

The patient, while lying flat, was not distressed in any way, but, on sitting upright, he became faint and began to sweat. The pulse was 100 per minute, blood pressure 80/60, and the heart sounds were normal, temperature 99° F. There was a left-sided pleural effusion extending to the sixth rib posteriorly which displaced the mediastinum to the right. A portable chest X-ray confirmed the presence of the effusion and showed a small apical pneumothorax not detectable on clinical examination. The patient was observed for several hours, during which time his condition did not change.

A thoracentesis was then performed and the effusion was partly emptied by the withdrawal of three and a half pints of sanguineous fluid. Following this, the patient felt better, and the blood pressure was recorded at 110/70. After centrifuging the pleural fluid it was found that one-third of the volume was red blood corpuscles. There was no evidence of further bleeding. Five days later the pleural cavity was finally emptied by the withdrawal of three pints of similar fluid.

Four weeks after admission the chest was clinically normal and a tomograph of the left lung showed no abnormality. Subsequently it has been found that culture of sputa and gastric washings has failed to grow tubercle bacilli. In the earlier stages of the illness systemic penicillin was administered and the iron deficiency anæmia resulting from the hæmorrhage was corrected by intramuscular iron.

This man, when seen recently, was in good health, and had returned to work.

#### COMMENT.

This complication of pneumothorax, when it does occur, is most often found in otherwise healthy men between 15 and 45 years of age (Calvert and Smith, 1955). Difficulty may be found in making the correct diagnosis. An acute abdominal condition is not an infrequent "first diagnosis" (Ross, 1952). In our case it was only after the finding of a pneumothorax on chest film that the true nature of the condition was suspected and later confirmed by thoracentesis. In the first instance, in spite of the pleural effusion, it was felt that duodenal hæmorrhage was the cause of the shock; an impression supported by the patient's history of indigestion.

It has been pointed out (Sellors, 1945) that immediate and repeated aspiration, although decreasing the intrapleural pressure, does not restart bleeding and will prevent fibrothorax. Results in this case agree with this statement. Where bleeding does not stop spontaneously, blood transfusion and thoracotomy may be necessary. Clyne and Hutter (1955) regard the condition as a surgical emergency and go so far as to recommend emergency thoracotomy as the treatment of choice in all cases.

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### **REVIEW**

MANAGEMENT IN OBSTETRICS. By Andrew M. Claye, M.D., F.R.C.S., F.R.C.O.G. Second Edition. (Pp. x + 218; figs. 35. 18s.) London: Oxford University Press, 1956.

This is the second edition of a book which has earned well-deserved popularity. It is intended for the general practitioner and gives advice on obstetrical management. This advice is backed by the wide personal experience of the author, and the methods of treatment recommended are those which he personally has found most useful; a most important feature.

The book is delightful to read, and the quotations which head many of the chapters make one envy the author his capacity for remembering the apt phrase and his extensive knowledge of English literature.

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The editors have brought together sixteen other American authorities to discuss various aspects of applied respiratory physiology in the field of emphysema. The book is of great value in presenting in one volume the many aspects of this work, and could be read with profit by all physicians who have a keen interest in the treatment of what is one of the most important diseases in this country. It is, of course, a must for the worker in experimental respiratory physiology, but for the ordinary doctor or student the many pearls that are to be found in over five hundred pages are somewhat obscured by both its length and lack of unity. As is admitted by the editors, different points of view are to be found amongst the contributors, and to the tyro this may be somewhat confusing. It is a series of important monographs, in which there is a certain amount of overlapping, so that it requires reading two or three times to get a sense of continuity.

The dangers of CO, retention are well emphasized, although there is not full agreement between the contributors as to immediate gravity of this in the presence of a normal hydrogen ion concentration maintained by adaptive mechanisms. The rôle of increased work of breathing in the accumulation of CO, is well stressed, as are the evils of decreased lung tension and subsequent check valve closure of the bronchii in expiration. It is perhaps in the field of alleviation of symptoms that this book has its greatest value. The help that may be given without upsetting homeostasis by gradual increments in continuous oxygen therapy and commencing with 1-2 litres per minute has been pointed out by Barach. The importance of restoring diaphragmatic function and the use of the 20° head-down position, both in this respect and in bronchial drainage, are probably not generally recognised, and this is well presented. The proper uses of bronchodilators and prednisone are brought out. Considerable discussion is given to the effects of mechanical methods-cough machines and the use of continuous and intermittent positive pressure apparatus, leaving one in rather mental whirl as to their practical importance. Diagrams and descriptions of apparatus used are somewhat sketchy if one wishes to know the mechanical details. Papers on the rôle of surgery, the influence of infection and the use of drugs are presented. It is of interest to see that potassium iodide and ipecacuanha still hold a place, although there are dangers in the former if hyperkalæmia should result from respiratory acidosis.

Opinions on the use of diamox to reduce bicarbonate and  $\mathrm{CO}_2$  are conflicting; the editors consider the resulting metabolic acidosis to be a contraindication. Final chapters on cor pulmonale and respiratory function tests are included, although the latter is somewhat incomplete. Nevertheless, a case has been made out for the proper control of treatment of these patients with even limited pulmonary function tests, and this volume will be of great value to those applying these methods previously academic to ordinary hospital medicine.

A. P. G.

THE EYE IN GENERAL PRACTICE. By C. R. S. Jackson, M.A., B.M., B.Ch.(Oxon.), D.O.M.S., F.R.C.S.(Ed.). (Pp. viii + 152; figs. 25. 21s.) Edinburgh and London: E. & S. Livingstone, 1957.

This book of 148 pages is well set out, the print is good and the illustrations quite adequate. The subject matter covers what a G.P. and medical student should know. It does not attempt to describe operations, complicated methods of examination or any treatment of a highly specialised nature.

The teaching, on the whole, is sound, but it is a pity that the modern classification of glaucoma has not been adopted.

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The publication of a fifth edition of this work, which was first published in 1945, is an indication of its usefulness to all nurses preparing for the certificate of the British Tuberculosis Association. Excellent detailed information is given in the earlier chapters on the more general aspects of tuberculosis and the morbid anatomy of the disease is clearly explained. The chapters devoted to the cause of the disease, together with the account of the symptoms and complications and associated diseases, are set forth in detail, and yet in a manner very easily assimilated by the nurses.

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A MANUAL OF HUMAN ANATOMY. By J. T. Aitkin, M.D., G. Causey, M.B., F.R.C.S., J. Joseph, M.D., M.R.C.O.G., D. A. Scholl, B.Sc., and J. Z. Young, M.A., F.R.S. Vol. 1: Thorax and Upper Limb (pp. viii + 162; figs. 36. 16s.); Vol. 2: Head and Neck (pp. viii + 180; figs. 53. 14s.); Vol. 3: Abdomen (pp. viii + 135; figs. 29. 12s. 6d.); Vol. 4: Lower Limb (pp. viii + 117; figs. 36. 12s. 6d.); Vol. 5: Central Nervous System (pp. vii + 140; figs. 40. 12s. 6d.) Edinburgh and London: E. & S. Livingstone, 1956 and 1957.

THESE five volumes represent a courageous and intelligent attempt to teach "anatomy without tears" by cutting out a vast amount of detail, and by close correlation throughout the text of structure, function, and clinical application. The manuals are a pleasure to read; the print is clear, the diagrams are simple and useful and are obviously the result of long teaching experience. The instructions for combining osteology and living anatomy with the dissecting-room work are admirable, and the accounts of lymphatic drainage are very good.

The plan attempted for each region is a brief general introduction, bringing out broad functional issues and often explaining structural patterns on simple embryological lines. This is followed by dissection instructions, enlivened with functional correlates and clinical applications. After this, further structural information is given concerning facts which are not so easily verified in the dissecting-room. Finally, functional aspects are once again considered, together with further practical applications. A separate chapter on lymphatic drainage follows the account of each major sub-division of the body. At the end of each volume instructions for practical classes in osteology and living anatomy are given.

The scheme, as a whole, is admirable; yet in practice the manuals fail, because the dissection instructions are too general and superficial and too quickly presented, affording an insufficient guide to the floundering student. The difficulties of actual dissection and identification are glossed over. Moreover, the information given, while excellent as regards each separate organ, does not convey a feeling for the region as a whole, for general relationships are not sufficiently stressed. It would be difficult for the average student from these books to synthesise the information into a useful whole.

On the credit side the manuals are light and easily handled and the ring binding makes them stay open. In spite of the manuals having been written primarily for the dissecting-room, in fact, I believe they would be very much more useful for rapid revision at the end of each period of dissection—with one exception—volume 5 on the Central Nervous System is very good, indeed, and could be strongly recommended for neurology practical classes, not least for its stimulating modern approach. If the dissecting instructions in the other manuals could be greatly amplified I believe the work would be very acceptable to the more intelligent students.

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There are nine chapters in the book, which is of 137 pages, and of these the ones dealing with the anatomy of the region and the distribution of analgesic solutions are outstanding.

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The author has based this report on his doctorate thesis and on additional cases and has, in all, examined 1,050 specimens from 636 cases. Of these 103 were from cases of malignant disease and in 73 malignant cells were found. No false positives were reported. His work is, therefore, of considerable value and diagnostic accuracy. As with all exfoliative cytology, the issue is not so much the value of the method under such conditions, but about its potential value and economic limitations in laboratories in general, where it would have to be entrusted to less experienced and less interested workers.

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TEXTBOOK OF PHYSIOLOGY AND BIOCHEMISTRY. By G. H. Bell, J. N. Davidson, and H. Scarborough. Third Edition. (Pp. 1068. 60s.) Edinburgh and London: E. & S. Livingstone, 1956.

This is now a standard textbook for medical students throughout the English-speaking world. The combined work of a physiologist, a biochemist, and a physician has resulted in a clear account of present-day physiological concepts. Advances in medicine are largely attributable to advances in the basic sciences, and the student who reads this book intelligently will have no difficulty in applying its contents to clinical practice. He may regret the fact that sixty-six pages have been added to the third edition, but the additional material, mainly concerned with body fluids and electrolytes, is amply justified. The book can be recommended to those working for higher degrees or diplomas.

J. T. S.

## ESSENTIAL UROLOGY. By Fletcher H. Colby, M.D. Third Edition. (Pp. ix + 656; figs. 358. 64s.) London: Baillière, Tindall & Cox, 1956.

The third edition of Essential Urology retains the character and style of the previous editions. The embryology, anatomy, and physiology of the genito urinary organs are first described. This is followed by a section on the examination of the urological patient. The final section deals with diseases of the urogenital tract. The diseases of each organ and recent advances in treatment are described.

At the end of each chapter numerous references have been added.

The book is ideally suited to the needs of the senior student and young surgeon interested in urology. It is admirably written and illustrated, and a pleasure to read.

J. M. M.

# EMERGENCIES IN MEDICAL PRACTICE. Edited by C. Allan Birch, M.D., F.R.C.P., D.P.H., D.C.H. Fifth Edition. (Pp. XII + 684; figs. 155. 37s. 6d.) Edinburgh and London: E. & S. Livingstone, 1956.

The need for a fifth edition of this book in eight years gives some indication of the many recent changes in standard medical practice. Its publication is a tribute to the industry of the editor and his panel of contributors in their task of keeping pace with these advances. The book has been extensively revised and the chapters on psychiatric, dermatological and renal emergencies have been rewritten. Its 696 pages contain a remarkable fund of essential, valuable, interesting and unusual information relating to the whole range of medical emergencies. The articles are clearly and concisely written, while printing and illustration are of a high standard. Backed by a comprehensive index, the detailed cross-reference system incorporated in the text greatly facilitates rapid consultation, and this is in keeping with the whole purpose of the book.

In a treatise covering such a wide range of subjects minor defects are inevitable, but detract little from its considerable overall value. The continued use in the 1956 edition of the term "bottle" in connection with fluid and electrolyte replacement is surprising, while unnecessary confusion may result from apparently haphazard references to pints and litres. Little is said of the rôle of 1-noradrenaline in the management of shock, whereas the traditional use of nikethamide and leptazole is described. The method by which quinidine is prepared for intravenous administration in the treatment of paroxysmal ventricular tachycardia is no longer a contemporary procedure. A simple scheme of heparin dosage, preferably in tabular form, would probably be of value as a guide to enforced domiciliary ant coagulant therapy and the range of oral preparations might well be widened.

This excellent book should be readily available in all casualty departments and acute reception units. It is strongly commended to doctors in general and hospital practice alike as a dependable and valuable ally in emergency.

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This is now a standard textbook for medical students throughout the English-speaking world. The combined work of a physiologist, a biochemist, and a physician has resulted in a clear account of present-day physiological concepts. Advances in medicine are largely attributable to advances in the basic sciences, and the student who reads this book intelligently will have no difficulty in applying its contents to clinical practice. He may regret the fact that sixty-six pages have been added to the third edition, but the additional material, mainly concerned with body fluids and electrolytes, is amply justified. The book can be recommended to those working for higher degrees or diplomas.

J. T. S.

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The third edition of Essential Urology retains the character and style of the previous editions. The embryology, anatomy, and physiology of the genito urinary organs are first described. This is followed by a section on the examination of the urological patient. The final section deals with diseases of the urogenital tract. The diseases of each organ and recent advances in treatment are described.

At the end of each chapter numerous references have been added.

The book is ideally suited to the needs of the senior student and young surgeon interested in urology. It is admirably written and illustrated, and a pleasure to read.

J. M. M.

# EMERGENCIES IN MEDICAL PRACTICE. Edited by C. Allan Birch, M.D., F.R.C.P., D.P.H., D.C.H. Fifth Edition. (Pp. XII + 684; figs. 155. 37s. 6d.) Edinburgh and London: E. & S. Livingstone, 1956.

The need for a fifth edition of this book in eight years gives some indication of the many recent changes in standard medical practice. Its publication is a tribute to the industry of the editor and his panel of contributors in their task of keeping pace with these advances. The book has been extensively revised and the chapters on psychiatric, dermatological and renal emergencies have been rewritten. Its 696 pages contain a remarkable fund of essential, valuable, interesting and unusual information relating to the whole range of medical emergencies. The articles are clearly and concisely written, while printing and illustration are of a high standard. Backed by a comprehensive index, the detailed cross-reference system incorporated in the text greatly facilitates rapid consultation, and this is in keeping with the whole purpose of the book.

In a treatise covering such a wide range of subjects minor defects are inevitable, but detract little from its considerable overall value. The continued use in the 1956 edition of the term "bottle" in connection with fluid and electrolyte replacement is surprising, while unnecessary confusion may result from apparently haphazard references to pints and litres. Little is said of the rôle of 1-noradrenaline in the management of shock, whereas the traditional use of nikethamide and leptazole is described. The method by which quinidine is prepared for intravenous administration in the treatment of paroxysmal ventricular tachycardia is no longer a contemporary procedure. A simple scheme of heparin dosage, preferably in tabular form, would probably be of value as a guide to enforced domiciliary ant coagulant therapy and the range of oral preparations might well be widened.

This excellent book should be readily available in all casualty departments and acute reception units. It is strongly commended to doctors in general and hospital practice alike as a dependable and valuable ally in emergency.

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