THE DOSAGE OF DIGITALIS.

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Historical.

Digitalis is one of the best known examples of drugs which have a "cumulative action." This implies that owing to its slow rate of excretion the drug, as ordinarily administered in repeated doses, may eventually amount to a sufficient quantity to cause symptoms of poisoning. This fact was well known to Withering⁽¹⁾ over a hundred and fifty years ago. In his classical publication entitled "An Account of Foxglove and some of its Medical Uses, with Practical Remarks on Dropsy and other Diseases" (Birmingham, 1785) Withering said, "Let the medicine be continued until it either acts on the kidneys, the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any one of these effects." Evidently it was also clear to this author that the beneficial action of digitalis could be expected to persist for a considerable time after discontinuing the drug. In order that improvement in the cardiac action may be maintained by the use of digitalis without the appearance of toxic symptoms, a daily dose must be found which will just balance the quantity of the drug destroyed and excreted. If the dose be too small the heart-muscle will gradually "recover" from the effects of previous digitalization and clinical evidence of an impaired cardiac reserve will become obvious, viz., dyspnoea on exertion and increasing dropsy. On the other hand, if the dose be too large, cumulation will occur and anorexia, nausea, vomiting, bradycardia, etc., inevitably appear. Clearly, therefore, the importance of accurate information on this subject can hardly be exaggerated.

During the past decade, interest in dosage with digitalis has centred in attempts to bring the heart under control as rapidly as possible with large quantities of the drug usually in the form of the tincture. Comparatively little clinical work has been undertaken on the rate of elimination of digitalis *in man*, with a view to establishing what might be regarded as a satisfactory "maintenance dose." Pardee⁽²⁾ has made some clinical observation on this subject. A slight modification of his procedure may be outlined as follows:—

1. Decide upon a dosage sufficient to produce cumulative effects in a given case, e.g., 1 c.c. of the tincture of digitalis thrice daily.
2. Suppose signs of overdose appear on the twelfth day.
3. Discontinue the administration of the drug for five clear days.
4. Recommence digitalization (1 c.c. t.i.d.) on the eighteenth day of the investigation.
5. Suppose the same symptoms of over-dose reappear at the end of the twenty-first day.

The following deductions may be made from these observations. In the second course of treatment the amount of tincture given was 12 c.c. This, therefore, was the quantity required (a) to replace the tincture excreted during the 5 days during which the drug was withheld, and (b) to make good the loss which continued when the drug was resumed from the 18th to the 21st day inclusive (4 days). Hence the rate of excretion per day $\frac{12}{4} = 3$ c.c. Pardee concludes "the average figure of 22 minims per day would afford a fairly satisfactory basis for long continued digitalis medication, since in only half the cases would it be much more or much less than the patient's ability to dispose of the drug."

A fair comment on these conclusions seems to be that, if the rate of excretion of digitalis is so variable from one individual to another, the suggested basis for a maintenance dose has a very limited value in practice.

Schmoll⁽⁹⁾, working on this subject, found that a daily dose of O.l.g. of digitalis leaf (equivalent to about 1 c.c. of the tincture by modern standards) was sufficient to exert a therapeutic action on the heart. Furthermore, he maintained that no poisonous effects could result from this dose because it was also the quantity excreted daily.

The findings of Pardee and of Schmoll mentioned above are quoted in modern textbooks of pharmacology. Thus, Cushny⁽⁴⁾ states that "the average patient destroys or eliminates the equivalent of from 1 to 2 c.c. of the tincture daily, so that to maintain an individual in full digitalization it is necessary to give about this amount of the drug (1.5 c.c. of the tincture daily)." Micks⁽⁵⁾ gives the same figures (1-2 c.c. of the tincture daily) as the rate at which the drug is destroyed. He states that a dose of more than 1 c.c. per diem will probably produce cumulative effects, while less than 1 c.c. daily "is likely to be inefficacious except as a maintenance dose." The author emphasizes the fact that "the amount (of digitalis) destroyed in the body is variable and the maintenance dose should be ascertained for every patient individually." Robinson⁽⁶⁾, in an exhaustive review of the therapeutic use of digitalis comments on our scanty knowledge of the fate of digitalis in the body and states that "the importance of this subject warrants its further clinical investigation."

The research recorded below was undertaken to obtain further information regarding the rate of excretion of digitalis in man.

Personal Observations.

Details relating to the data obtained are set out in Table II appended.

Observations were carried out on 36 consecutive patients, 27 of whom were females and 9 males. The ages of five of the patients were between twelve and sixteen years but all the other patients were adults. It will be seen that some form of cardiac abnormality was present in nearly every case. In No. 19, however, chronic bronchitis was the principal disease and no lesion was apparent on examination of the heart. Premature beats were the only abnormal feature of Case No. 24. A high proportion of the patients suffered from the effects of hypertension—14 in the group—and bundle-branch block was detected in two instances.

Preparation and Dosage of Digitalis Employed. Digitalis leaf (Burroughs and Wellcome) was used in preference to the tincture. The administration of the drug in tablet form ensured greater accuracy as most of the patients were treated from the Outdoor Department. One grain of the leaf was given twice daily. The dose therefore amounted to 1.2 international units per diem and this was equivalent to 1.2 c.c. of the tincture, or approximately 20 minims a day.

Procedure of Investigation. A clinical examination was made and an electrocardiogram obtained immediately before beginning the administration of digitalis. The salient features of these preliminary observations are mentioned briefly in the left-hand columns of the Table II given below (p. 165).

As a rule the drug was administered for about a fortnight. Not infrequently, however, it was found necessary to discontinue it well within this period. On the other hand, a few patients received digitalis leaf for four and even five weeks. The patients were instructed not to make any alteration in their habits regarding work, exercise, etc., but to take particular notice as to "whether the tablets made them

any better or any worse." This phraseology was adopted in an attempt to eliminate the effects of *suggestion*—which is a well-known factor in the favourable results obtained from some "special" form of treatment.

Clinically, the changes which were regarded as indicating digitalization were (1) diminished breathlessness, (2) relief of substernal discomfort associated with effort, (3) bradycardia, and (4) disappearance of oedema (if any). These may be called the beneficial results or therapeutic effects of digitalis administration. In some cases, however, as will be seen from the Table (p. 165), the drug produced toxic effects, i.e. nausea and vomiting, excessive bradycardia (less than 60 per minute); palpitation, drowsiness and even the aggravation of signs of cardiac failure (See notes on Cases 12 and 22).

Further electrocardiograms were taken at weekly intervals. The effect of digitalis upon the electrocardiogram has been worked out thoroughly during the past twenty years as a result of the work of Cohn, Fraser and Jamieson.⁽⁷⁾ A slurred appearance of the RST complex develops early. Subsequently a diphasic wave occupies the S-T interval and finally the T-wave becomes inverted. In addition to these myocardial effects interference with conduction may be found and in particular prolongation of the PR interval sometimes accompanies this change. In view of the gross changes in the T-wave which can be produced readily by digitalis medication, it is surprising that evidence of depression of auriculo-ventricular conduction is often so slight.

Results.

Varying degrees of clinical evidence of digitalization of the heart were found in 53 per cent. of the series and electrocardiographic changes occurred in 70 per cent. of the 36 patients. Clinical changes indicating digitalization sufficient to produce a considerable increase in the cardiac reserve (as judged by the criteria mentioned above) may be accepted as convincing evidence of cumulation, no previous "intensive" treatment having been given. The association of clinical and electrocardiographic changes was seen in 42 per cent. of the patients. In these cases the electrocardiographic evidence may be justifiably regarded as confirmatory of the clinical observations. On the other hand, in 8 patients (Nos. 13, 14, 18, 19, 23, 26, 27 and 34) representing 20 per cent. of the whole series, the electrocardiographic changes, though quite definite, were unaccompanied by therapeutic or toxic effects. While there can be no doubt that the dosage was sufficient to affect the heart muscle in these patients it cannot be assumed that cumulation was taking place.

Absence of any alteration in the electrocardiogram during the administration of these small doses of digitalis was exceptional. No change attributable to the drug was found in 14 per cent. of the group (Nos. 20, 24, 26, 28 and 29). The same cases, with the addition of No. 21, were also those in which no clinical changes—subjective or objective—were detected.

Twelve patients (Nos. 4, 5, 8, 9, 10, 11, 12, 17, 21, 22, 30 and 31) developed one or more of the toxic effects enumerated above. This was preceded by a stage in which therapeutic and beneficial actions were appreciable in all but three of the patients. In Nos. 10, 12 and 31 a toxic effect was the first change noticed. The cardiac disability in patient No. 12 was actually aggravated by the drug and subjective and objective evidence of cardiac failure appeared. There was no history of any additional exertion, etc., to account for the sudden change, and the evidence of cardiac insufficiency disappeared on discontinuing the drug. In Nos. 10 and 31 the usual gastric symptoms of overdose with digitalis occurred without any significant change in the cardiac condition. The findings in one of the patients (No. 1) suffering from the effects of bundle-branch block were inconclusive.

Six suitable patients were later selected from the group to test the action of one grain of digitalis leaf daily. The following is an abstract of the results obtained (Table I).

TABLE I.

Effect of Digitalis Leaf—I gr. daily:

No.			Clinical Manifestations.
5	...	...	Nausea and vomiting.
8	...	...	Dyspnoea abolished.
10	...	...	Nausea and vomiting.
14	...	...	No change in electrocardiogram.
15	...	...	Dyspnoea less troublesome.
32	...	...	Bradycardia.

The last case (No. 32) was one of auricular fibrillation with mitral stenosis and aortic incompetence. Cardiac reserve was so slight that movement in bed made the patient breathless. Without digitalis the heart-rate (apex beat) was about 60 per minute. Two or three days after receiving one grain of digitalis leaf twice daily the pulse rate fell to 50 per minute and the drug was discontinued on the 6th day. Subsequently the same effect was produced by giving (a) one grain daily (b) one grain on alternative days. It appeared that as the cardiac reserve diminished the susceptibility to digitalis increased.

Summary and Conclusions.

With doses of not more than 2 grains of digitalis leaf daily 75% of the patients showed electrocardiographic evidence of "digitalization".

In about half the number in a series of 36 patients, this dose was enough to produce clinical evidence of increased cardiac reserve. Confirmation of these results was obtained on repeating the investigation in 6 of the patients using a dose of only one grain of leaf daily.

This investigation seems to justify the following conclusions:

1. The rate of excretion and/or destruction of digitalis in the tissues varies greatly from one individual to another.
2. The rate is considerably less than 2 grains of digitalis leaf per diem (equivalent to 20.3 minims or 1.2 c.c. of the tincture) in the majority of patients.
3. Individual variations are sufficient to justify the statement that for practical purposes no useful rule exists regarding the maintenance dose of digitalis. The individual requirements must be estimated by the process of trial and error. The well established practice of giving 5-10 m. of the tincture twice or thrice daily and subsequently adjusting the dose as may be required by the individual patient recommends itself on the grounds of experimental work in man. This does not apply to the immediate treatment of cases of acute congestive heart failure where a dose of 2-3 drachms of the tincture of digitalis should usually be administered at once, but to the subsequent stabilization of such cases under the influence of the drug.

It is a pleasure to record my thanks to Dr. John Gracie, Visiting Physician to the Western Infirmary of Glasgow, for permission to publish the records of some of the patients in this series.

REFERENCES.

- 1.—Withering, *An Account of Foxglove and some of its Medical Uses, with Practical Remarks on Dropsy and other Diseases*, Birmingham, 1875.
2. Pardee, Jour. Am. Med. Assocn. 1919, lxxiii, 1822.
3. Schmolli, Amer. Jour. Med. Sc., 1911, cxli, 35.
4. Cushman, *A Textbook of Pharmacology and Therapeutics*. 10th Ed. Revised by Edmunds and Gunn. London. Churchill, 1934.
5. Micks, *The Essentials of Materia Medica, Pharmacology and Therapeutics*, 1st Ed. Churchill, 1935, pp. 227-228.
6. Robinson, *Medicine*, 1922, 1, 1.
7. Cohn, Fraser and Jamieson, Jour. Exp. Med., 1915, xxi, 593.

Table II.—Details of Observations on Patients receiving Digitalis Leaf, grs. 2 daily.†

No.	Sex.	Age.	Diagnosis.	Heart—Physical Signs.	Heart failure (Subjective or objective).	E.C.G. before digitalis.	Days at gr. 1 b.d.	Clinical change.	E.C.G. after digitalis.	Toxic action of digitalis.	Remarks.
1	F.	62	Myocardial degeneration.	Very big heart. Triple rhythm.	Continuous dyspnea aggravated by exertion.	Right bundle branch block.	14	Incr. dyspnea, headache, and tightness in chest. Heart I.S.Q.	No change	Incr. dyspnea. No nausea. Tightness in chest.	No benefit from digitalis leaf, but previously noted subjective improvement after Nativelle's granule gr. 1/600 b.d. Harmful effect of digitalis not conclusive owing to onset of "common cold."
2	F.	50	Myocardial degeneration.	No enlargement. Premature beats.	Dyspnea on exertion.	Low voltage and almost abs. Tl. P.B.s.	14	Gen. condition improved. Not definite re. dyspnea.	S ₂	Bradycardia 60. Occasional nausea.	"Cramps around heart and in back" while taking digitalis.
3	M.	50	Hypertension. B.P. 195/110.	Left side much enlarged.	Slight dyspnea on exertion.	Left ventricular preponderance. P.B.s (auric.).	7	Less dyspnea.	No change	None.	
4	F.	45	Hypertension. B.P. 200/90.	Left side much enlarged.	Slight dyspnea on exertion.	L.V. + Within normal limits	7	Less dyspnea for a few days. (? suggestion).	T ₁ . S ₂ .	Nausea. No vom. Frequent watery diarrhoea 6th day.	
5	F.	57	Hypertension. B.P. 240/120.	Both sides much enlarged.	Slight dyspnea and cyanosis on exertion. Pain sub-sternal and down L. arm.	L.V. + PR 0.22 sec.	14	Less dyspnea; other symptoms unchanged.	S ₁ . S ₂ . PR 0.24	Nausea.	Continued to 28 days. Dig. gr. 1 or gr. 2 daily in last 14 days. Nausea more troublesome and severe vomiting occurred.

†Significance of various signs used in table.

P = PR interval increased.

T = inversion of T wave.

B = bradycardia.

Numbers 1, 2, 3 refer to Leads.

S = characteristic change in ST complex.

TABLE II.—Continued. A.

No.	Sex.	Age.	Diagnosis.	Heart—Physical Signs.	Heart failure (Subjective) or objective).	E.C.G. before digitalis.	Days at gr. 1 b.d.	Clinical change.	E.C.G. after digitalis.	Toxic action of digitalis.	Remarks.
6	M.	53	Angina of effort.	Main cardiac impulse epigastric. Tactac rhythm.	Marked dyspnoea on exertion and gripping sensation in chest.	T ₂ and T ₃ inverted. Spreading Q.R.S.	14	Less dyspnoea during first week. Improvement not so marked in 2nd week.	T ₁ more marked	None.	In 3rd and 4th weeks, 3 gr. daily to maintain improvement. Pain in chest on exertion unaffected.
7	F.	35	Mitral stenosis and auric. fibrilln.	Classical signs.	Dyspnoea on exertion	Auricular fibrilln.	14	Less dyspnoea.	S ₂ more marked—slight change	None.	Improvement about the same as after Nativelle's granules gr. 1/600 b.d.
8	F.	41	Mitral stenosis.	Classical signs.	Dyspnoea on exertion.	Slurred QRS ₂ .	18	Improvement: less dyspnoea espec. in 2nd week.	S ₂	Nausea and vomiting from 18th day.	Maintenance dose gr. 1 digitalis per diem. Dyspnoea—even on moderate exertion—abolished by this amount.
9	F.	46	Auricular fibrilln. Mitral stenosis.	Both sides of heart enlarged.	Persistent diarrhoea. Objective failure occasionally.	Auricular fibrilln.	14	Improvement in dyspnoea.	B. S ₃ .	Nausea and vomiting after 14 days.	Dyspnoea and epigastric discomfort reappeared one week after stopping digitalis gr. 1 t.i.d.
10	F.	64	Hypertension.	Left side enlargement.	Dyspnoea only on exertion.	Within normal limits.	7	No change.	No change	Vomiting.	Subsequently gr. 1 daily for one week resulted in nausea.
11	F.	—	Adherent pericardium.	Left side enlarged. Lesion fully compensated.	Able to avoid all symptoms.	Normal complexes PR 0.2 sec.	7	Dyspnoea aggravated	S ₁ S ₂	None.	Digitalis stopped after one week.
12	F.	45	Hypertension. Angina of effort.	Both sides enlarged.	Dyspnoea on exertion, otherwise well compensated.	Slurred QRS 2 and 3, otherwise normal record.	7	Compensation upset. No change in dyspnoea.	—	Nausea. Insomnia. Abdominal pain. Edema of feet. Palpitation.	Harmful effect of digitalis was quite definite. Discomfort rapidly disappeared on stopping drug.

TABLE II.—Continued. B.

No.	Sex.	Age.	Diagnosis.	Heart—Physical Signs.	Heart failure (Subjective or objective).	E.C.G. before digitalis.	Days at gr. i b.d.	Clinical change.	E.C.G. after digitalis.	Toxic action of digitalis.	Remarks.
13	F.	45	Mitral stenosis.	R. side enlarged and $\frac{1}{2}$ in. on left. M_1 accentuated but no pre systolic bruit.	No dyspnoea but precordial pain troublesome.	PR 0.2 sec. Complexes normal.	17	Pain much relieved for 14 days then recurred.	S_1, B_{S_3}	Nausea. once.	B.P. 145/75. Headache and dizziness unaffected by digitalis.
14	F.	12	Chorea. Mitral stenosis.	Classical signs. Well compensated early case.	None.	Normal record.	34	None.	S_1, T_2, T_3	None.	Clinically unaffected by digitalis. Repeated later for ten days with same result.
15	F.	56	Hypertension. Myocardial damage. B.P. 220/105.	Big heart. Sounds of poor volume and quality.	Severe dyspnoea on exertion.	E.C.G. of R.B.B.B. but no spreading of Q.R.S.	14	Moderate improvement in dyspnoea.	S_2	None.	No effect during 1st week. Repeated for 1 week with a dose of 1 grain daily: improvement again reported.
16	F.	68	Hypertension and Angina of Effort.	Big heart. Tactac sounds and triple rhythm.	Pain and dyspnoea on exertion.	T inverted in all leads. Coronary art. dis.	14	Less dyspnoea.	S_1, S_3	None.	Pain in chest recurred about 10th day (climbing stairs). In 2nd E.C.G. effects of coronary artery disease were magnified.
17	F.	41	Mitral stenosis.	Classical.	Dyspnoea.	Within normal limits.	14	Less dyspnoea for two weeks then recurrence.	S_1, S_2, S_3	None except rate 60.	Gr. 3 daily resulted in nausea and vomiting. Polyuria following gr. 2 b.d. despite absence of cedema.
18	F.	60	Mitral stenosis and B.P. 196/90.	Classical. but both sides much enlarged.	Dyspnoea on exertion.	P.R. = 0.24 T_2 shallow inversion. Q.R.S. widened.	6	No change.*	T_2 (deeper) T_3	None.	Investigation repeated with digitalis gr. 1 daily for effect on E.C.G.

TABLE II.—Continued. C.

No.	Sex.	Age.	Diagnosis.	Heart—Physical Signs.	Heart failure (Subjective or objective).	E.C.G. before digitalis.	Days at gr. i b.d.	Clinical change.	E.C.G. after digitalis.	Toxic action of digitalis.	Remarks.
19	F.	43	Chronic bronchitis.	No apparent lesion.	Dyspnoea—prob. mainly pulmonary.	Normal.	14	Less dyspnoea but probably due to rest.	S ₂ (early)	None.	
20	F.	29	Hypertension 185/100 Subac. rheumatism.	L. side enlarged. 4½ in. from midline.	None.	L.V. otherwise normal.	14	None.	No change	None.	Receiving salicylates at same time.
21	F.	58	Hypertension.	L. side enlarged.	Dyspnoea.	Normal.	14	No improvement in dyspnoea.	S ₂ , S ₃ .	Palpitation.	Numerous neurotic symptoms complicate the history.
22	F.	62	Hypertension. Myocardial degeneration.	Both sides much enlarged.	Subternal discomfort and dyspnoea on exertion.	E.C.G. of R.B.B.B. but no spreading of Q.R.S. P.R. = 0.16 sec. Lead 1.	14	Discomfort and dyspnoea much improved.	S ₁ , T ₁ , flat-tented PR = 0.24 sec. Lead 1.	Severe palpitation	Never had palpitation before starting digitalis.
23	F.	36	Chronic bronchitis. Dry pleurisy.	Enlarged R. heart	Dyspnoea—mainly pulmonary.	Normal. PR = 0.16	28	No change.	PR = 0.2	None.	Clinical evidence of digitalization obscured by chronic bronchitis.
24	M.	64	Palpitation (P.B.)	No apparent abnormality.	None.	L.V. otherwise normal.	14	None.	No change.	None.	Discomfort of P.Bs. disappeared on bromides.
25	F.	45	Hypertension.	L. side enlarged 4½ in. from midline.	Breathlessness on exertion.	Poorly formed T ₁ —positive but shallow.	14	Less breathless.	S ₁ (early)	None.	Menopausal symptoms also.

TABLE II.—Continued. D.

No.	Sex.	Age.	Diagnosis.	Heart—Physical Signs.	Heart failure (Subjective or objective).	E.C.G. before digitalis.	Days at gr. i b.d.	Clinical change.	E.C.G. after digitalis.	Toxic action of digitalis.	Remarks.
26	M.	61	Hypertension. Myocardial degeneration B.P. 200/120.	Left side enlarged. 1st sound of poor quality.	Dyspnoea and sub-sternal pain on exertion.	L.V. + otherwise within normal limits. P.R. = 0.2 sec.	12	None.*	P.R. = 0.24 sec.	None.	
27	F.	30	Mitral stenosis with rheumatic pains in legs.	Classical signs.	Dyspnoea on exertion.	R.V. + P.R. = 0.22 sec.	16	None.*	S ₁ , T ₁ , P.R. = 0.32 sec.	None.	
28	M.	60	Chronic myocarditis.	No enlargement but poor heart sounds and tic-tac at apex.	Anginal pain and dyspnoea on exertion.	T ₁ and T ₂ inverted.	(a) 10 (b) 14	None* (unreliable).	No change.	None.	
29	F.	53	Coronary artery disease. Hypertension.	Left side enlarged. Premature beats.	Dyspnoea on exertion.	L.V. + P.B.s Otherwise normal.	7	No improvement.	Coronary thrombosis.	None.	Developed coronary thrombosis about a week after beginning digitalis. Also suffering from chronic cholecystitis. E.C.G. effects of digitalis obscured by evidence of coronary thrombosis.
30	F.	14	Rheumatic carditis.	Left side slightly enlarged.	None.* Compensated.	Normal P.R. = 0.16 sec.	8	Bradycardia 64.	P.R. = 0.2 sec.	Nausea. Drowsiness.	Nausea disappeared on stopping digitalis.
31	F.	12	Rheumatic carditis.	Both sides enlarged.	None.* Compensated.	Normal.	8	None.	No change.	Nausea. Vomiting.	No further vomiting after stopping digitalis. Pulse rate fell as pyrexia subsided.

*Patients confined to bed during investigation.

TABLE II.—Continued. E.

No.	Sex.	Age.	Diagnosis.	Heart— Physical Signs.	Heart failure (Subjective or objective).	E.C.G. before digitalis.	Days at gr. i b.d.	Clinical change.	E.C.G. after digitalis.	Toxic action of digitalis.	Remarks.
32	F.	38	Mitral Stenosis. Failure of compensa- tion.	Both sides much en- larged. Fibrilla- tion.	Dyspnoea even while at rest.*	Fibrilla- tion	(a)6 (b)5	Bradycardia 50.	Brady- cardia.	No nausea.	Digitalis gr. i daily for 8 days also produced bradycardia (50 per min.).
33	M.	14	Rheumatic carditis.	Left side slightly enlarged.	None. Compensa- ted.	Normal.	11	None.	Brady- cardia.	None.	
34	M.	48	Chronic bronchitis. Myocardial degenera- tion.	Both sides enlarged.	Anasarca.	RV+ PR=0.22 sec.	12	None.	T _s , PR= 0.22.	None.	
35	M.	64	Myocardial degenera- tion.	Muffled heart- sounds. Outline indefinite. (Pleural effusions).	Anasarca.	Inversion of T ₁ and T ₂ .	20 (gr. 1)	Steady im- provement.	No change	None.	
36	M.	16	Mitral stenosis and subac. infective endocard- itis.	Enlarge- ment mainly on left side.	None*. Compensa- ted.	Normal.	10	No change.	No change	None.	