PART III

THE EFFECT OF PITUITARY IMPLANTATION IN BREAST CANCER AND COMPLICATIONS OF IMPLANTATION.

CHAPTER XII

THE EFFECT OF YTTRIUM-90 IMPLANTATION ON ADVANCED BREAST CANCER

Endocrine ablation for inoperable breast cancer began with the classical publication by Sir George Beatson in 1896. He showed that oophorectomy could cause disease remission. Then in 1951, Huggins and Bergenstal showed that remissions could also be obtained by adrenalectomy, and West and his colleagues (1952) showed that adrenalectomy could still induce remissions in oophorectomised patients. Luft and Olivecrona (1953) were the first to report on hypophysectomy, and found that this too could induce remissions.

In this chapter, the response of breast cancer to yttrium-90 implantation is to be detailed, and compared with the reported results of hormone therapy, oophorectomy, adrenalectomy, and pituitary destruction. Many patients in this series had previously received some of these alternative endocrine therapies and their responses will be indicated.

One of the problems immediately encountered in reporting on breast cancer response is the establishment of criteria which are sufficiently detailed to allow no alternative assessment in a given case. Hitherto, most authors have evolved their own criteria, and this makes comparison of results qualitative only. A major source of difficulty is the fact that in a given patient it sometimes happens that the various manifestations of the cancer show different responses. Because of this an attempt was made to take this into consideration in defining new criteria and grades of response. This finding of variation of cancer response in a given patient is recognised by most other workers, and is allowed for by the "mean clinical value" assessment method of Atkins and his colleagues (1960). In the assessment of cancer response to be made in this chapter, conventional observations were used; measurements of urinary calcium and various serum enzymes will not be utilised as their validity are controversial, or need further assessment. They will be separately analysed in Chapters XIII and XIV respectively.

A second, and independent way in which the results can be assessed and different series compared, is to examine survival data. The responders can be compared with the non-responders, assuming that the non-responders indicate the expected survival in the untreated disease.

A premise upon which the method of assessing to be reported in this chapter is based, is that the site of a metastasis has no effect upon its likelihood to respond to pituitary ablation. This has been questioned by McCalister and his colleagues (1961), who believe that skeletal deposits are more likely to respond than those in soft tissues. This point will be considered from the present series; no objection to the premise is shown.

An important practical objective is to establish the minimum ablation required for some cancer response. Most authors have total ablation as their objective, and this is to a certain extent supported by the poor cancer remissions from stalk section (Connolly and Connel, 1958). In earlier chapters, criteria were set up for pituitary function tests that imply at least 90% anterior pituitary necrosis; it will now be shown that if these criteria are met, the best possible cancer response can be expected. The length of survival will be compared with the I-131 test, which yields a numerical result suitable for this type of analysis.

Finally, a number of features will be investigated which might influence the success of the operation, such as response to previous endocrine therapy, age of the patient, and duration of her disease.

METHOD OF STUDY

Parameters used for cancer response assessment.

A. Objective response.

It was the aim in this project to obtain the following evidence of cancer activity before and after implantation.

Radiographs were taken of affected bones and pulmonary deposits 3-monthly. Routinely, patients had pre-operative x-rays of the skull, chest, dorso-lumbar spine, and pelvis, as well as any bones clinically suspected of metastatic involvement. When the patients had died, all available serial radiographs were inspected in chronological order without reference to the film dates or date of implantation. A decision was made as to which films showed the first improvement and relapse. In many cases, serial films wereavailable for some time before implantation. A condition was established that for a change to be recorded, it must be evident in at least two serial films unless it was very marked indeed. Special care was taken to disregard areas which had been treated with deep x-ray in the past. All assessments were made personally; after independent initial reviews by the writer and a consultant radiologist, the final assessments were agreed.

A particular problem was encountered in patients in whom a post-implant x-ray revealed a new sclerotic lesion at a site which was perfectly normal in previous films. This could represent the appearance of a new osteoblastic metastasis (i.e. a deterioration) or the healing of a previously inapparent osteolytic lesion (i.e. an improvement). It soon became apparent that if this type of appearance occurred in a patient with only osteolytic lesions pre-implant, it was commonly associated with the healing of other skeletal deposits. Accordingly, the rare finding after implantation of a new lesion which was osteoblastic was recorded as a healing lesion if there had been no osteoblastic lesions pre-implant, and as unassessable if there had been osteoblastic deposits pre-implant.

Serum calcium was measured in the routine laboratory by flame photometry (MacIntyre, 1957 and 1961). 95% of normal subjects between the ages of 20 and 50 years have values between 4.9 and 5.4 mEq./l. The error of the method is under 2%.

Blood samples were usually obtained on three occasions before implantation. After implantation, tests were done every few days during the first few weeks, and then about 3-monthly. A fall in serum calcium was recorded as an improvement if it fell from an elevated mean pre-implant level to normal.

Serum alkaline phosphatase was measured in the hospital routine laboratory by the method of King and Wootton (1956a). The normal range (95% of adults) is 3.3 to 12.9 K-A u. (King-Armstrong units). Measurements were made on the same blood samples as were taken for serum calcium.

A change indicative of cancer response was recorded if the serum alkaline phosphatase showed a distinct rise and then a fall. The exact criteria used for response are defined in Chapter XIII: when the pre-implant value is under 20 K-A u. and a rise to above 30 K-A u. occurs between the 14th and 31st day, and falls again to under 20 K-A.u.by the 120th day, a cancer response is recorded.

Blood smears and haemoglobin estimations, were serially followed in patients with leukoerythroblastic anaemia pre-implant. An improvement was recorded if the haemoglobin rose to normal, and primitive cells could no longer be found.

Visible or palpable lesions were measured before implantation, and periodically thereafter.

Miscellaneous lesions such as papilloedema (which was photographed) from intracranial deposits, and liver size, were noted serially.

B. Subjective response.

Change in symptoms, such as bone pain and lassitude, were noted.

Grading of cancer response.

Patients dying within 28 days were regarded as unassessable. The cancer response was graded by the following criteria. They were created so as to leave a minimum of ambiguity when the individual patients were considered.

A. Objective grades of response.

Grade A: All lesions present at the time of implantation showed regression, and no new lesions or abnormalities appeared before the regression was evident.

Grade B response: Clear regression in most of the original lesions, but a few did not improve, or even showed an advance, or a few new lesions appear; however, the overall picture was improvement.

Grade C response: Arrest for six months, i.e. there was no change in the original lesions and no new ones appeared.

Grade D response: Clear regression in some lesions, but simultaneous appearance of others, so that the overall position was unchanged.

Grade E: a few lesions regressed but many advanced or appeared, so the overall picture was cancer deterioration.

Grade F response: All lesions advanced.

Grade G response: Insufficient observations to make an assessment (usually patients dying in the first month).

B. Subjective grades of response.

Grade I response: Striking improvement in symptoms and entirely worthwhile.

Grade II response: Definite improvement, but value to patient doubtful.

Grade III response: No obvious improvement.

Grade IV response: Not assessed (because of death within a month, or follow-up not possible).

For the purpose of some later analyses, the response grades will be grouped, so as to provide three groups of larger numbers, as follows:

Responders: Grades A and B

"Mixed" responders: Grades C and D.

Non-responders: Grades E and F.

RESULTS

The incidence of objective response of breast cancer to yttrium-90 implantation (Fig. XII.1).

A total of 53 women with disseminated breast cancer which was relapsing after any previous endocrine therapy were submitted to needle-implantation between 16/7/57 and 28/4/61, and personally supervised up to death. There was but one survivor at the time of writing (April 1963). The few patients treated by transcranial yttrium-90 implantation were not included in this particular analysis, although followed up and assessed in the same way. In each case, the objective grade of response and pituitary function tests were examined, and compared with survival. Where two implants were done (11 cases), only the events following the second were considered.

Grade of cancer response:- Upon the criteria defined under "methods", all cases were assigned into grades A to G. In the event, no instances of a grade E response were found ("mainly advancing disease, but a few lesions improving"). As there were only three cases with a grade C response, these have been combined with the eight with a grade D response, which should be of somewhat comparable significance, for the purpose of this analysis.

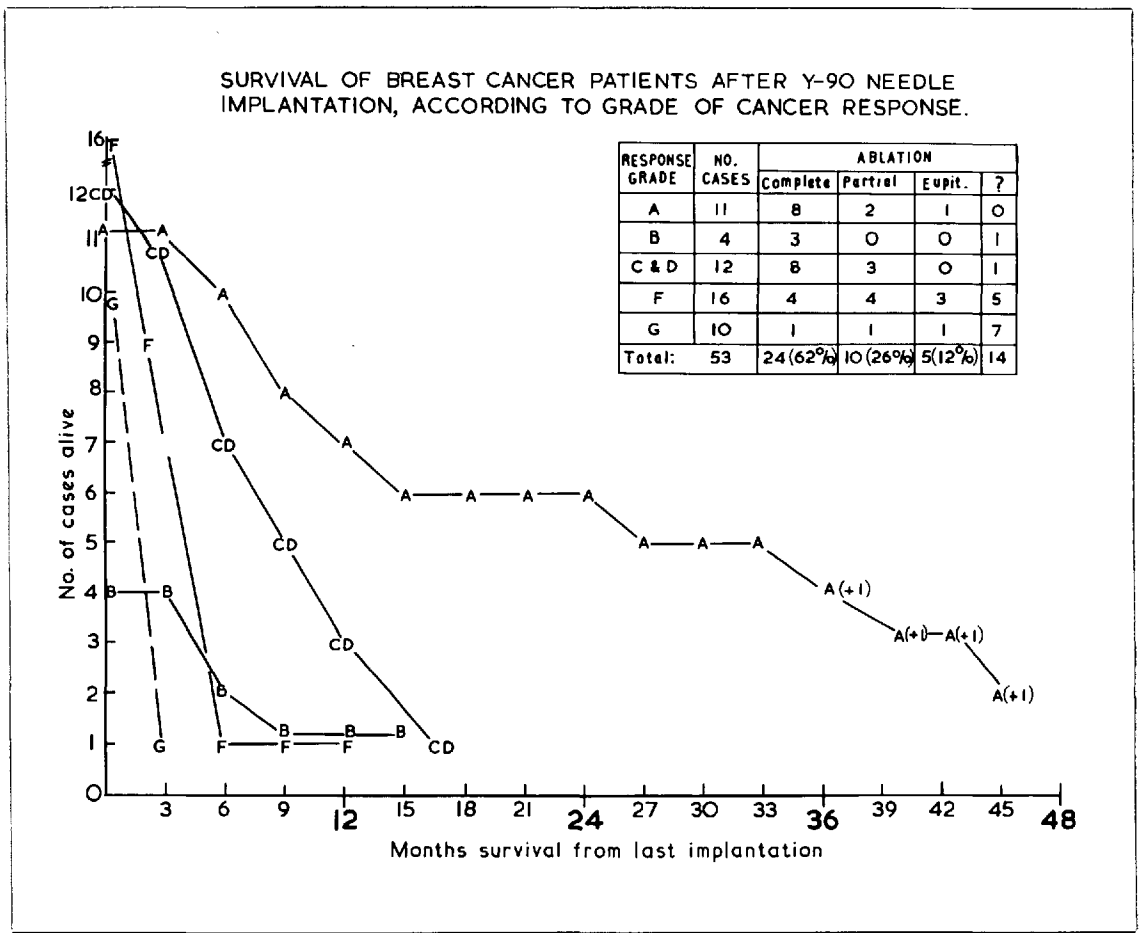
Degree of ablation:- In each case, all the pituitary function data were examined, and the degree of ablation assigned to one of four categories.

"Complete" - both the mean of all I-131 uptakes done after the 14th day was under 21%*, and the patient was found to be clinically steroid dependent, supported by a W.D.T. of under 40%.

"Partial" - only one of these two test criteria were satisfied, while the other fell short of the defined level.

"Ineffective ablation" - neither the mean I-131 fell to below 21%, nor was the patient steroid dependent clinically.

* one patient who developed frank myxoedema with a mean neck uptake of 21% was placed in this grade.



RESPONSE GRADE	NO. CASES	ABLATION			
		Complete	Partial	Eupit.	?
A	11	8	2	1	0
B	4	3	0	0	1
C & D	12	8	3	0	1
F	16	4	4	3	5
G	10	1	1	1	7
Total:	53	24 (62%)	10 (26%)	5 (12%)	14

Fig. XII.I. The survival of 53 patients after implantation is shown according to grade of objective cancer response. Only the grade A responders obtained worthwhile extension of life.

"?" - tests incomplete, usually due to early death.

The results are all shown in Fig. XII.I. The table, drawn as an inset, shows that 62% of the patients in whom pituitary function tests were done had had a "complete" ablation. Eleven out of the 43 (26%) cases in which the cancer response was assessed enjoyed a grade A response, while 27 of the 43 (63%) had some objective effect. It is of considerable interest that there was one patient (C.Ke.) with a grade A response who required neither thyroxine nor steroids. Unfortunately she died from an unrelated condition in a few months (as did two other grade A responders).

The survival data is shown graphically in Fig. XII.I. It is at once evident that the Grade A responders survived longer than the others, and form the only group with survivors of more than 15 months. The extent and rapidity of advance of the cancer of the 16 patients with a grade F response (i.e. no detectable response) who survived over 28 days might be considered to give an estimate of the life-expectancy without pituitary implantation; none survived beyond a year. Against this, there were more than half of the grade A responders alive after a year, but only one of the grade B responders. Expressing these results in a different way, the mean survival for the grade A responders was 92 weeks, and for the grade F responders was 14 weeks; this represents an extension of life of 18 months in the most responsive group. Worthwhile prolongation of life is confined to the grade A responders; only one patient in the whole series survived over a year without a "complete" functional ablation.

<u>The incidence of subjective response of patients with breast cancer after treatment by yttrium-90 implantation.</u>

As defined under "Methods", the same 53 patients were also assessed into subjective grades of response. These largely reflect changes in well-being and bone pain. The results are shown in Table XII.I.

TABLE XII.I.

THE SUBJECTIVE RESPONSE TO PITUITARY IMPLANTATION

		SUBJECTIVE GRADE				
		1	2	3	4	Total
OBJECTIVE GRADE	A	10	1	0	0	11
	B	1	2	0	1	4
	C & D	2	8	0	2	12
	F	0	2	12	2	16
	G	0	2	3	5	10
	Total	13	15	15	10	53

It is evident that a good subjective response was practically confined to those whose objective response was grade A, while "no better" was almost the rule where there was no objective response. However, occasional first-class subjective improvements were found in patients whose objective response was not entirely satisfactory. The overall picture, as seen from the patients' point of view was that about one third (13 of 43) would have thought the procedure entirely worthwhile.

A comparison between the post-implant I-131 test and survival (Fig.XII.2)

The mean of all I-131 uptake tests done at least a fortnight after the last implant is shown plotted against survival from that implant in Fig. XII.2. The untreated life expectancy for most of these patients is probably under six months, judging from the grade F responders of Fig. XII.I., and is indicated in Fig. XII.2 by a vertical interrupted line.

There are 20 patients surviving for six months or more. All had a 48-hour neck uptake of under 23%, all but three being below 18%.

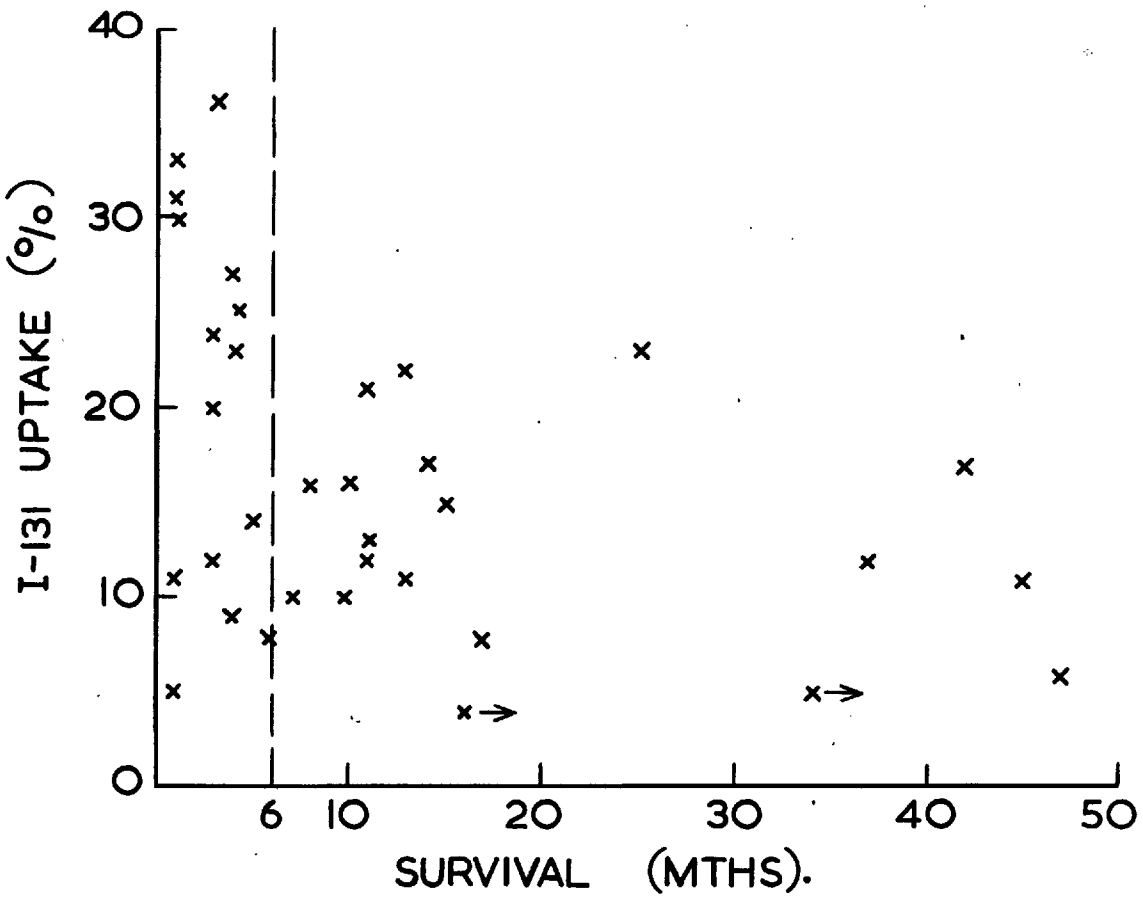


Fig. XII.2. The mean I-131 uptake is compared with survival after the last implant. The vertical interrupted line is drawn at the limit of life-expectancy for most of the unresponding patients.

When the three patients with uptakes above 17% were scrutinised, it was found that all had developed obvious clinical myxoedema, so it becomes clear that for significant extension of survival, the I-131 uptake should be depressed to a level which will cause myxoedema, and this usually means a neck uptake of under 21%, implying over 90% pituitary necrosis.

Effect of patient's age upon grade of cancer response (Table XII.II)

The cancer response was assessed in 32 patients having "partial" or"complete" ablation, who survived over a month from implantation, and had the cancer response assessed. The results are shown in Table XII.II. No obvious connection between age and response grade is shown.

TABLE XII.II.

EFFECT OF AGE UPON CANCER RESPONSE

CANCER RESPONSE GRADE	AGE AT IMPLANTATION (Yrs.)			
	35-44	45-54	55-64	65-74
A	4	2	2	2
B	0	2	1	0
C & D	1	5	4	1
F	1	4	3	0

Effect of duration of the cancer upon disease response (Table XII.III & Fig.XII.3)

A total of 34 patients with "partial" or "complete" ablation in whom the cancer response was assessed, had the probable duration of the cancer recorded. In nearly all cases, this was the date that the

COMPARISON OF SURVIVAL AFTER IMPLANTATION WITH DURATION OF CANCER (34 PATIENTS)

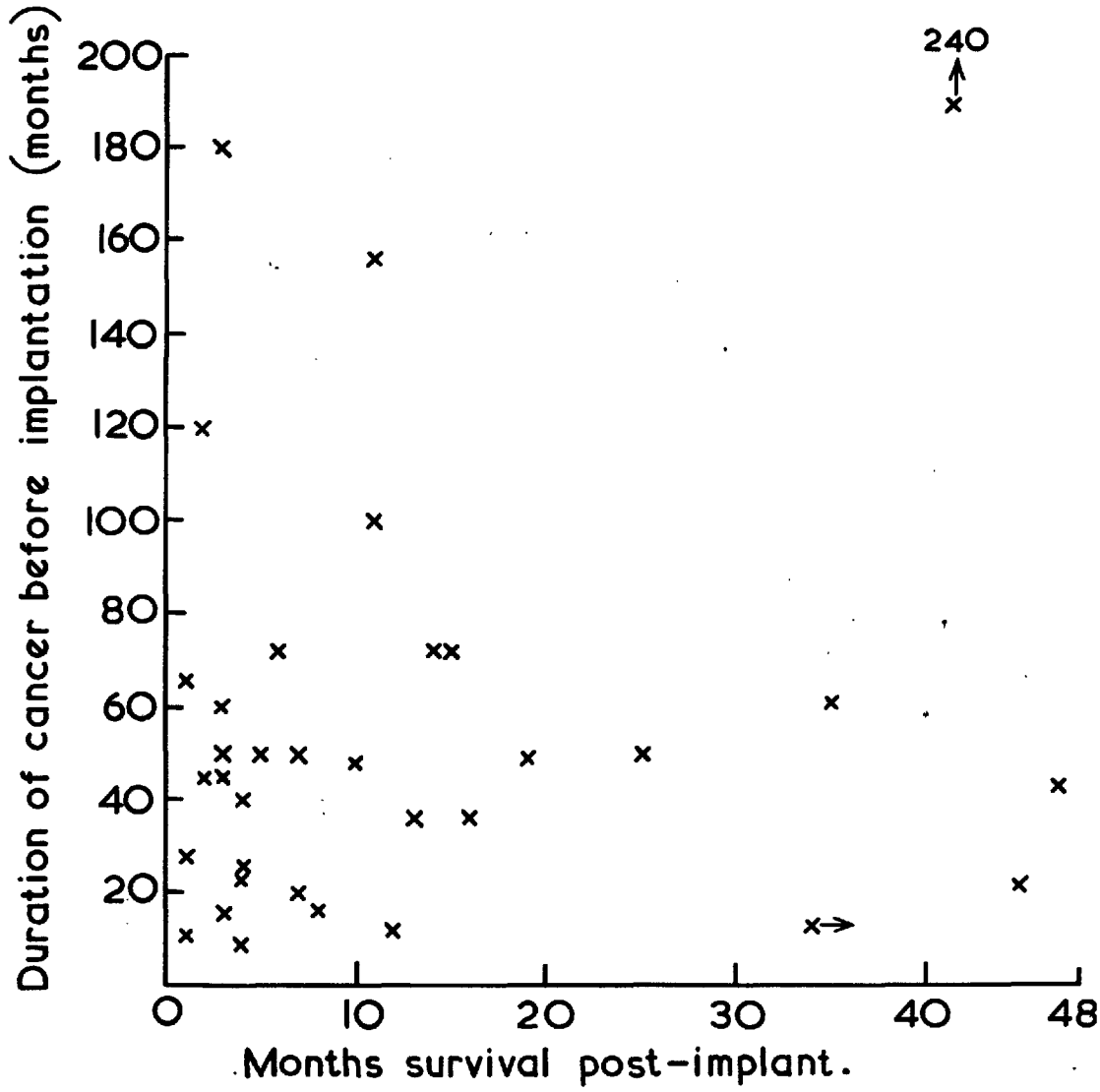


Fig. XII.3. All these patients had an implant, causing "partial" or "complete" functional ablation.

patient discovered a lump in the breast.

The results are shown in Table XII.III.

TABLE XII.III.

EFFECT OF DURATION OF CANCER UPON CANCER RESPONSE

CANCER RESPONSE GRADE	DURATION OF CANCER AT IMPLANTATION (MONTHS)					
	0-24	25-48	49-72	73-96	97 - 120	>120
A	5	1	3	0	0	2
B	2	1	0	0	0	0
C & D	3	3	3	0	1	1
F	1	4	3	0	1	0

In 34 patients having a "partial" or "complete" pituitary ablation, the survival and the duration of the disease before implantation were known.

It can be seen in Table XII.III and Fig. XII.3 that there is no striking correlation between cancer duration and either response grade or survival.

Effect of response to previous endocrine therapy on response to pituitary implantation.

The cancer response to "partial" or "complete" pituitary ablation was assessed in 37 patients in whom the effect of previous endocrine therapy had been recorded. Several patients had received more than one form of endocrine treatment. Nearly all had had their previous endocrine therapy elsewhere, and the response was usually recorded by the referring physician as simply "yes" or "no"; the patients came from many different physicians, and the standards and objectivity

of assessment were largely unknown. No correlation was found; this could be attributed to variable and imprecise assessment of the initial response to initial endocrine manipulation.

The effect of site of metastases upon likelihood of response to pituitary ablation (Table XII.IV)

A total of 34 patients with either "partial" or "total" pituitary ablation had an objective assessment of cancer response. For this purpose, any improvement in any part of a lesion was recorded as "objective remission".

The results are shown in Table XII..IV. The remission rate for patients with bone metastases was 13 out of 23, while for patients without bone metastases was 6 out of 11. Thus, no greater sensitivity of bone involvement to implantation is manifest.

Table XII.IV.

The Effect of Site of Metastases upon Cancer Response

		Total patients	Objective remission
Osseous	Bone only	11	8
	Bone and local	4	2
	Bone and visceral	8	3
		23	13
Non-osseous	Local only	2	2
	Visceral only	4	2
	Local and visceral	5	2
		11	6

To test this further, a group of 14 patients with needle-implantation and two patients with trans-cranial implantation who had both bone and non-bone deposits were analysed. Seven of these patients showed bone healing after implantation, and all these showed soft tissue healing as well. The converse also held. Thus, in a given patient

the secondaries are just as likely to heal, whether in bone or soft tissue.

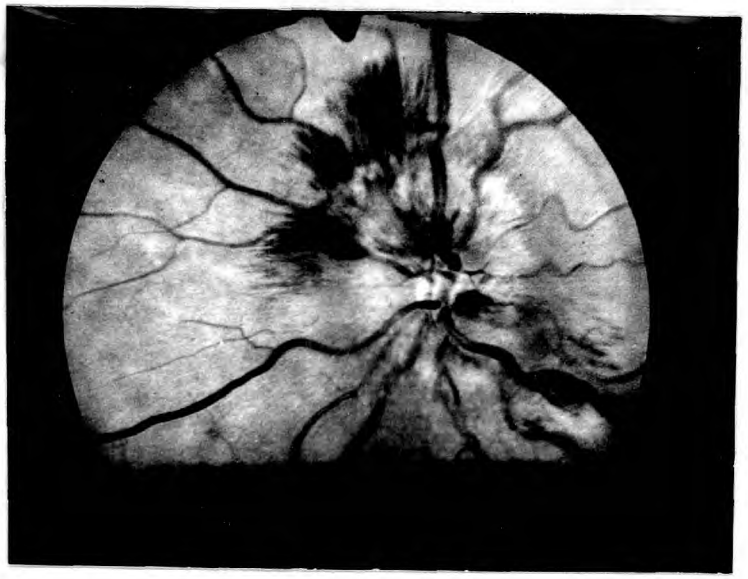
It has variously been reported (e.g. McAlister et al.,1961) that lesions in non-osseous sites respond less well. The results of the present series do not support this. In particular, raised intra-cranial pressure has been a contraindication to transcranial hypophysectomy (Atkins, 1963). In contrast, two patients with advanced papilloedema from cerebral deposits showed complete clinical recovery after implantation. An example was case F.Pr., presenting with drowsiness and advanced papilloedema, who obtained a complete clinical remission,and at six weeks the fundi were normal. The papilloedema recurred during the terminal relapse. These retinal changes were photographed and are shown in Fig. XII.4. Case P.Fl, in addition to losing papilloedema after implantation, also showed a striking shrinkage of hepatic deposits, as shown at autopsy (Fig.XII.5). She had previously enjoyed an excellent response first to irradiation-induced menopause and then to adrenalectomy. Complete adrenal excision was confirmed at autopsy.

<u>The effect of a second yttrium-90 implantation upon breast cancer in patients having an incomplete ablation from the first implant.</u>

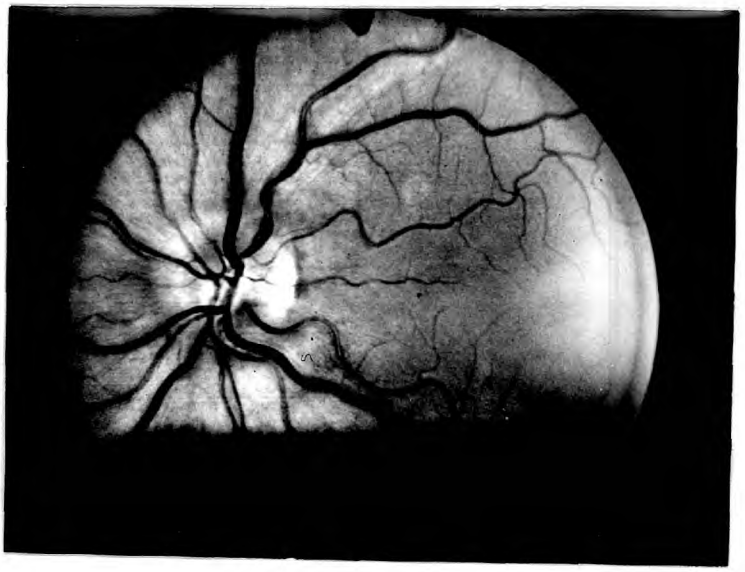
(<u>Tables XII.V and XII.VI.</u>)

Undoubtedly the most precise data for establishing the optimum degree of functional pituitary ablation for breast cancer response would be obtained from an analysis of a series of patients having first a partial and later a more complete ablation. In this way, whenever the second implant caused an additional regression, the degree of ablation from the first could be regarded as insufficient.

Among the 53 patients having an yttrium-90 implant between 16/7/57 and 28/4/61, there were 11 who had more than one implant. Among these 11 patients, there were four in whom both the cancer response to the first implant was assessable, while the second implant caused an objective and subjective improvement.



pre-implant



6 weeks post implant

Fig. XII.4. Photographs of the left optic fundus showing resolution of papilloedema during cancer remission induced by Y-90 implantation. The papilloedema returned when the patient finally went into terminal relapse.

Fig. XII.5. Autopsy appearance of cut surface of liver in case P.Fl. Striking fibrosis and shrinkage of the deposits has occurred. The irregular surface is caused not by the presence of cancer tissue projecting superficially, but by the contraction of deposits producing fissures.

The endocrine findings in this group of four very important cases are summarised in Table XII.V. and the cancer response data in Table XII.VI. All four patients had an additional objective and subjective response to the second implant, although all had had some response from the first implant. Therefore, in all cases, the degree of ablation from the first implant was adequate for some benefit, but insufficient for the best results. In no case did the first implant reduce the I-131 uptake sufficiently to cause myxoedema, while all tested after the last implant reached this degree of ablation. Further, in no case did the first implant reduce adrenal function to the point of clinical steroid dependence, while all but one did reach this criterion after the last implant.

From this it can be concluded that partial ablation will not cause the best cancer result. We have no information about whether a greater degree of ablation than that which only just meets the specified endocrine criteria would induce an even better cancer remission; this could only be decided from the results response to re-implantation of a series of patients in whom these endocrine criteria had already been met by the first implant.

TABLE XII.V.

THE ENDOCRINE DATA OF FOUR PATIENTS HAVING MORE THAN ONE IMPLANT FOR BREAST CANCER

Patient	NUMBER & DATE OF IMPLANT	EFFECT ON THYROID FUNCTION					EFFECT ON ADRENAL FUNCTION					EFFECT ON F.S.H. (m.u./24hrs.)
			Evidence of subthyroidism				Steroid withdrawal assessment					
		Mean I-131 uptake (%)	Months after implant	Clin. myxoedema	Highest chol.ast. (mg.%)	E.C.G. Change	Duration of steroid withdrawal	W.D.T. (best figure after 4 days)	Effect on E.C.G.	Mean 17 KGS (mg/24hrs.)	Effect clinically	
O.Wi.	1st 28/11/57	27	4	No	204	No	4 mths.	104%		16	None	
	2nd 21/4/58	40	4	No	314	No	4 mths.	112%	No	17	None	>12, <48
	3rd 1/12/58	23	3	Yes	405		8 days	46%		1	Marked	
L.Du.	1st 27/10/59	35	2	No	240	No	9 days	122%		3	None	
	2nd 22/1/60	5					several weeks		No		None	
F.Br.	1st 11/3/60	26	2	No	220	No	7 days	49%	Yes	7	None	< 12
	2nd 20/5/60	9*	3	No	390		5 days	14%		0	Marked	
F.Pr.	1st 19/8/60	40	7	No	200	No	4 weeks	120% too ill	No	6	None	~12
	2nd 14/4/61		2½	No	190	No	4 days			**	Marked	< 6

* done on 13th day.

** plasma 11 OHCS was 1.9µgm/100ml.

TABLE XII.VI

CANCER RESPONSE DATA OF FOUR PATIENTS HAVING MORE THAN ONE IMPLANT FOR BREAST CANCER

PATIENT	IMPLANTS	OBJECTIVE	SUBJECTIVE
O.Wi.*	first 28/11/57	Bone 2^{o} more numerous at 2 mnths, and worse at 4 mnths.	No loss of bone pain
	second 21/4/58	Bone 2^{o} calcifying at 3 mnths; further improvement at 5 mnths. New 2^{o} at 7 mnths.	Pain disappeared temporarily.
	third 2/12/58	Bone 2^{o} calcifying at 2 mnths; further improvement at 7 and 15 mnths; I.S.Q. at 22 mnths.	"Permanent"loss of pain.
L.Du.	first 27/10/59	Bone 2^{o} unchanged at 3 mnths. Serum Ca. fell to normal and relapsed.	Bone pain improved and relapsed.
	second 22/1/60	Bone 2^{o} calcifying strongly at 21 mnths. and further at 28 mnths. Serum Ca fell to normal "permanently"	Bone pain "permanently" lost.
F.Br.	first 11/3/60	Breast mass and ulcer unchanged at 2 mnths. and bone 2^{o} calcifying.	Bone pain improved.
	second 20/5/60	Breast mass and ulcer almost disappeared at 3 mnths and further calcification of bone 2^{o}.	Became pain-free.
F.Pr.	first 18/8/60	Papilloedema gone by 6 weeks, recurred at 8 mnths. Some bone 2^{o} healed while others appeared.	Resumed consciousness and returned to work.Relapsed
	second 14/4/61	Papilloedema disappeared and recurred terminally.	Partial improvement in lucidity.

* further details of the cancer responses of this patient are given in Appendix I.

DISCUSSION

Although the cause of breast cancer in the human female cannot be discovered from the study of other mammalian species, the principles that have been found to govern certain aspects of breast neoplasia in animals are of considerable interest. One of the earliest such observations was that of Lathrop and Loeb who in 1916 reported that oophorectomy could prevent the development of cancer in the females of certain strains of mice that were specially prone to breast cancer. Then in 1932, Lacassagne showed that the administration of oestrogens could induce breast cancer even in male mice. In addition to hereditary predisposition and endocrine factors, a transmissable factor in the milk, known as the "milk-factor" has been found (Bittner, 1936) although only in mice. Rats can be made prone to breast cancer by the stomach-feeding of certain hydrocarbons (review by Noble and Cutts, 1959; Huggins and Yang 1962); the giving of both oestrogen and progesterone will increase the susceptibility to such cancer, while oophorectomy will afford protection. Similar findings using cutaneous applioations in mice had been reported by Jull (1954).

In the human female, a significant hereditary pronensss to breast cancer has not been shown (Murphy and Abbey, 1959). On the other hand, endocrine factors have been shown to be of some importance. For instance, a striking agreement between the age-incidence of breast cancer and the menopause was shown by Dawson (1932), while the occasional aggravation of breast cancer by oestrogen administration is well-known.

A slight but definite superiority of hypophysectomy over combined adrenalectomy and oophorectomy has been established by Atkins and his colleagues (1960) by the follow-up of parallel series, while the response to hypophysectomy of six patients who had already had a combined adrenalectomy with oophorectomy, has been shown by Ray and Pearson (1962) and a striking example was found in the present series (case P.Fl.). Thus the question of a pituitary factor is raised as well. The effect of both growth hormone and prolactin on human

breast cancer has been investigated. The effect of growth hormone on human breast cancer has been variable (Pearson and Ray, 1959; Lipsett and Bergenstal, 1960), as also has been the effect of ovine prolactin (McCalister and Welbourn, 1962) on the urinary calcium excretion of affected patients. The possibility of the latter being a test for hormone dependence was raised by the finding of higher calciuric effects in those who subsequently responded to hypophysectomy than in those who did not.

The remission rate of metastatic breast cancer found in the present series can now be compared with published reports. From a personal analysis of seven series of surgical hypophysectomies which embraced all the series with this data published by 1960 (Kennedy et al., 1956; Luft et al., 1958; Baron et al., 1958; Edelstyn, 1958; Andersson 1958; Cobb and Scoville, 1959; Pearson and Ray, 1960) came the finding that about one half (51.2% of 508 assessed cases) showed objective remission or arrest of the carcinoma. The mean survival of the responders was 17 months, or 12.4 months beyond that of the non-responding group (216 cases assessable). This extension of survival of about a year would be a slight underestimate as there were some patients still alive in each series. A similar proportion of responders was found in an analysis of four published series of patients treated by yttrium-90 needle implantation, totalling 149 patients; there were 48% with objective remission out of 112 patients whose data were given (Ellis et al., 1958; Moseley et al., 1958: Forrest et al., 1959; Notter, 1959). These figures can be compared with the present series, where 27 out of 43 (63%) patients assessed obtained some objective remission, or 50% of the total number treated irrespective of the degree of functional ablation. These overall response figures gathered from the literature suffer from a certain amount of variation in the standards adopted by the different groups of workers. The criteria of Pearson and Ray (1960) and Boesen and colleagues (1961) used for their two large series can be directly compared with those used in the present study, in that both groups separately quote regression rates for patients on

the criteria used here for the grade A responders. The two series give figures of 30% and 33% of assessable cases respectively, which can be directly compared with the figure of 28% (11 out of 43) found in the present study. Thus, it can be concluded with confidence that about a third of assessed patients obtain a good objective remission after pituitary destruction, whereas about one half of the patients obtain some response.

The mean survival of the "grade A" responders in both of these series was 18 months longer than the non-responders. A similar figure was found in the present series where the 11 grade A responders survived on average, for 21 months, whereas the 16 with no regression at all only survived three months, giving a prolongation of survival of 18 months. As all these data are in agreement, it can also be asserted that the fortunate one third of patients treated by pituitary destruction who obtain a grade A response, can expect on average, about 18 months extension of life.

The response rate from adrenalectomy has been widely found virtually identical to hypophysectomy. Response to other endocrine procedures have been reviewed by Pearson (1962). He found that about 40% of premenopausal patients respond to oophorectomy, and that lower response rates occurred and poorer remissions were obtained with androgens, oestrogens and prednisone. An extensive report on the results of androgen and oestrogen therapy was made by the Council on Drugs, Americal Medical Association, in 1960. 21.4% of 580 women responded to androgens, and 36.9% of 364 women responded to oestrogens. Prednisone alone, even in doses of 30 mg./day or more, would appear to induce little objective remission, as only two out of 52 patients showed radiological bone healing after a year of therapy in the series of Stoll, 1963; Gardner et al. (1962b), in reporting 24% objective regressions from prednisone 30mg. and tri-iodothyronine 50 µg. daily, also noted that calcification of osseous lesions was rare. The expected side-effects from this large dose of prednisone were indeed encountered. Tri-iodothyronine

in maximum tolerated dosage was found to be without effect by Emery and Trotter (1963). Combined hormone and chemotherapy seems more promising, although carrying a distinct hazard (Watson and Turner, 1959; Lyons and Edelstyn, 1962).

Of the factors which might indicate the response to hypophysectomy, the only one generally agreed upon is the response to oophorectomy.

From three series (Baron et al. 1958; Cobb and Scoville, 1959; and Pearson and Ray, 1960) it was found that 26 out of 30 women who responded to oophorectomy also responded subsequently to hypophysectomy, whereas only three out of 31 oophorectomy non-responders responded to hypophysectomy.

In contrast, patients who have already had an adrenalectomy will but rarely respond to hypophysectomy. There were only six remissions out of 43 such cases, gathered from the literature (Baron et al., 1958; Forrest et al., 1959; Notter 1959, Pearson and Ray, 1960).

Among the other factors which have been considered in the search for guides to the prognosis after hypophysectomy, the histology of the tumour has been found valueless (McCalister et al., 1961). The duration of the cancer was found by McCalister and colleagues and the present series to have no definite influence on cancer remission, although in their much larger series, Pearson and Ray (1960) found a slightly higher proportion of responders among the patients who had the disease for longer. A slightly better chance of response in those who have not reached the menopause was found by McCalister and colleagues (1961), and their review of the literature supported this. It has also been claimed that metastases in bone heal more readily than metastases in soft tissues (Pearson and Ray, 1960; McCalister et al. 1961); this could not be shown in the present series; presumably such a discrepancy could be as well explained by a superiority of radiological measurements of bone healing over the methods used to assess healing in soft tissues.

A number of tests have been proposed for the detection of the cases which will respond well, but most have been rejected. Three

seem to be of possible value, if further confirmed; the urinary steroid ratio aetiocholanolone: 17-hydroxycorticosteroids of Bulbrook and colleagues (1960); Hale's (1961) finding that those women whose cancer takes up radioactive phosphorus with periodicity or is influenced by exogenous hormones are more likely to respond, and the finding of McCalister and Welbourn (1961) that the women who have a greater calciuric effect from prolactin injections are more likely to respond.

The final point for discussion is the degree of ablation which is required for the best possible cancer response. The only data for consideration are those of the present study, where it was found that a minimum requirement was to reduce the I-131 uptake to below 21%, or to induce myxoedema and, equivalently, render the patient steroid dependent. These criteria imply at least 90% necrosis from yttrium-90 implants (Chapter IV). Whether a higher % necrosis would give a better cancer effect than this minimum objective, cannot be ascertained from this study.

SUMMARY

1. 53 women had yttrium-90 pituitary implantation for disseminated breast cancer. 43 had the cancer response evaluated objectively. 11 obtained regression of all evident metastases without the simultaneous appearance of new ones (grade A response), four showed mainly improvement, but also the simultaneous appearance of new deposits (grade B response), and 12 showed either arrest for six months (grade C response) or equal healing and cancer advance (grade D response). Thus, about half of the total number of patients treated showed at least some objective response.

2. The mean survival of the 11 grade A responders was 21 months, whereas the mean survival of the 16 patients who showed no response at all (grade F response) was three months, giving a prolongation of life of 18 months in this most favourable group (28% of those assessed). Survival was much shorter in the less satisfactory response grades.

3. Striking subjective response to implantation occurred in 13 patients, (about one third of those assessed) of whom 10 showed a grade A objective response.

4. Irrespective of the grade of cancer response, all of the 20 patients who survived over six months had an I-131 uptake of under 21%, or became clinically myxoedematous.

5. Four patients had a cancer response from a second pituitary implantation. All had had an incomplete functional ablation from the first implant, but had had a transient cancer regression. The second implant rendered three of them steroid dependent and all had an I-131 uptake below 21%.

6. It appears likely that if the degree of reduction of pituitary function is insufficient to induce myxoedema (or an I-131 uptake of under 21%) and steroid dependency, the cancer response is less

marked and shorter than if the functional impairment exceeds these criteria.

7. The following factors did not materially influence the cancer response; age of the patient, duration of the cancer, or site of metastases.

CHAPTER XIII

THE EFFECT OF PITUITARY IMPLANTATION ON THE SERUM AND URINARY CALCIUM AND ON THE SERUM ALKALINE PHOSPHATASE IN WOMEN WITH BREAST CANCER

Serial measurements of the serum calcium levels have been generally held to be a valid index of breast cancer progress when treated with various endocrine measures. On the other hand, although some have considered the urinary calcium to be also valid (e.g. Pearson, 1957; Myers and Bodansky, 1957), others have seriously challenged this belief (Gardner and Gordan, 1962). Serial measurement of the serum alkaline phosphatase has not been widely reported on for this purpose, and the criteria for interpretation have not been clearly defined.

It is the purpose in this chapter to examine the value of serial measurements of the serum and urinary calcium and serum alkaline phosphatase as indices of breast cancer activity, and to discover in which patients such measurements were appropriate, and to define criteria for interpreting change.

METHODS USED AND PATIENTS STUDIED

The chemical methods for the serum calcium and alkaline phosphatase have been considered in Chapter XII, page 305; the upper limits of normal are 5.5 mEq/l., and 13 K.A. units/100ml.

The urinary calcium collections were made directly into bottles containing 10 ml. conc. hydrochloric acid, and the estimations made by flame photometry as for serum calcium. Collections were made on the 4th and 5th days of a qualitative low calcium diet consisting of a normal diet with the exclusion of milk and milk products; this gives a calcium intake of about 500mg. daily.

A major problem when evaluating urinary calcium data is defining the upper limit of normal. On a diet with somewhat less calcium than used here, Bhandarkar and Nordin (1962) found that with

one exception, 13 normal subjects excreted under 14 mEq./24hrs.; on a free diet, all excreted under 20 mEq./24hrs. Gardner and Gordan (1962), using a diet identical to the one used in the present study found that most (95%) normal women excrete under 106mg/12hrs. which gives an approximate upper limit of normal of 11 mEq./24hrs. which is in close agreement with the finding of Knapp (1947). In view of this data, it would appear reasonable to set an extreme upper limit of normal at 15 mEq./24hrs. for the purpose of considering the present results, although most normal subjects excrete under 10 mEq./24hrs. The lower limit of normal would be about 2.0 mEq./24hrs. (Knapp, 1947). The necessity for a standard diet might be questioned. Although dietary calcium usually has but little effect on the urinary output, in some patients the effect is considerable (Spencer and Lewin, 1963).

The serum inorganic phosphate estimations were made on a Technicon autoanalyser, the method being based on that of Fiske and Subbarow (1925). The normal range, from the mean $\pm$ 2 S.D., is 1.4 to 2.6 mEq./l.

The grading of breast cancer response to implantation was done as described in Chapter XII.

The patients studied were all those women with breast cancer with adequate opportunity for data collection, treated by needle implantation between 16/7/57 and 28/4/61. In addition to these with needle implants, there were three patients with transcranial implants included in the present analysis. Only one patient with adequate data was excluded; she had primary hyperparathyroidism (case E.Co.). In all cases, a routine pre-implant skeletal survey was made, consisting of x-rays of skull, chest, lumbar spine and pelvis, as well as any bones suspected of involvement on clinical grounds.

RESULTS

Serum Calcium

Pre-implant levels (Table XIII.I).

A total of 63 women had both a measurement of serum calcium and a radiological skeletal survey done during the pre-implant assessment. In 41 of them, more than one (usually 3) measurements were made, and the mean taken. Several patients died before implantation could be done.

It is seen in Table XIII.I that 21% of patients had an abnormally high serum calcium, the extreme upper limit of normal being 5.5mEq./l. (MacIntyre, 1961). Half of these showed substantial levels of 6.1 mEq./l or above. When the patients are divided into those the 46 with radiological bone deposits and 17 without, it is seen that all the patients with raised serum calciums had bone involvement.

TABLE XIII.I

THE FREQUENCY OF RAISED SERUM CALCIUM BEFORE IMPLANTATION IN 63 PATIENTS : CORRELATION WITH BONE METASTASES.

	Numbers of patients				% of patients >5.4 mEq./l	
	Total	Serum Ca (mEq/l.)				
		<5.5	5.5 to 6.0	>6.0		
Bone deposits	46	33	7	6	28%	21%
No bone deposits	17	17	0	0	0%	

The effect of pituitary implantation on the serum calcium (Fig.XIII.I).

In 40 pituitary implantations, serum calcium levels were obtained before implantation and were subsequently followed at least to the point when the objective cancer response could be graded on criteria other than biochemical measurements of calcium metabolism. Survival in all patients was more than 28 days. When a patient had more than one implant, each was treated as having its own series of observations.

Patients' objective cancer response were graded as in Chapter XII,

into "good responders", "mixed responders", and "non-responders". There were no grade E responders.

For the purpose of analysing the serial serum calcium data in Fig.XIII.I., each patient's progress was divided into phases, so that all the serial values for a given phase could be expressed as a single mean value. The pre-implant phase included all observations made in the pre-implant assessment. The second phase began arbitrarily on the eighth post-operative day; it terminated at the onset of cancer relapse in the case of those who were "good"or"mixed" responders, and at death in the case of the "non-responders". There was a third phase in the case of the "good responders" and the "mixed responders", commencing at the onset of cancer relapse, and terminating at death. The date of commencement of relapse in those with initial responses was obtained from clinical observations, radiographs, and very occasionally by the date on which serum calcium began to rise.

All the results are shown in Fig. XIII.I. The patients have been divided into two groups on the basis of the pre-implant serum calcium level. Above, are shown the data of 29 patients with a normal pre-implant serum calcium, and below are shown 11 patients with raised initial levels. In the inset are shown three hypercalcaemic patients whose general post-implant response was unassessed.

It is at once evident that no significant change occurred in those with normal levels before implantation. On the other hand, nearly all the hypercalcaemic group showed a fall in serum calcium to normal when the disease responded, and all four followed into terminal relapse showed a terminal rise.

When the serum calcium levels of the 21 patients followed into relapse are examined in this phase, it is seen that all 7 who had raised levels at this time, also had raised pre-implant levels. No patient developed hypercalcaemia after reaching the stage in her disease when implantation was performed. Hence it appears that the factor which determines whether a patient will develop hypercalcaemia

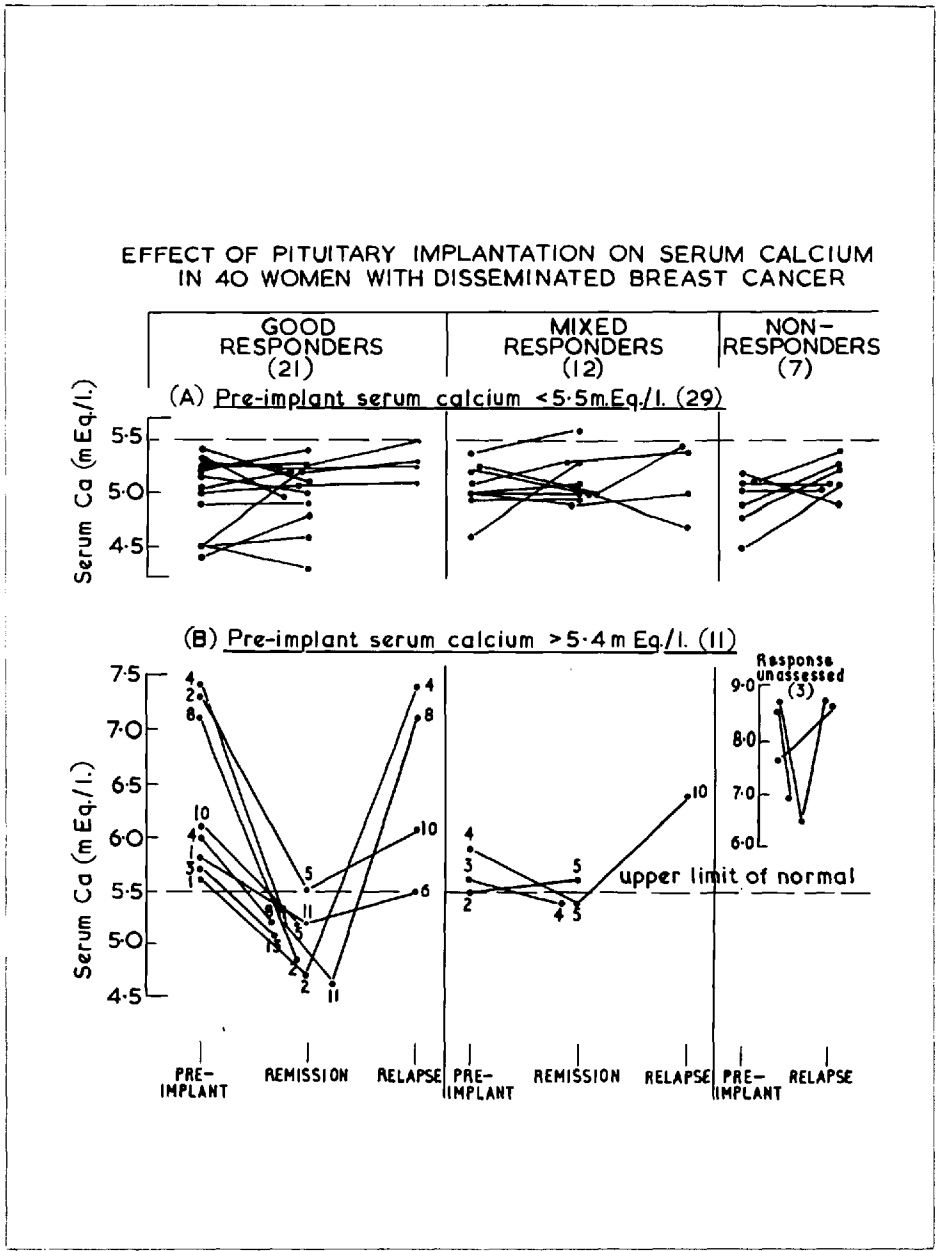


Fig. XIII.1 - Each plot is the mean of all estimations in a patient while in the phase indicated at the foot of the figure. The number of observations from which the means were calculated is shown for those with high values before implantation.

is already exerting its influence at the time that multiple metastases appear.

It may thus be concluded that the only patients in whom useful information about cancer progress may be obtained from the serum calcium are those in whom there is a raised level before implantation. A clear fall into the normal range, and subsequent rise appear to faithfully reflect cancer response and relapse. A post-implant fall in serum calcium is most unlikely to be a non-specific consequence of implantation, as small(terminal) rises occurred in five of the seven non-responders. There were no hypercalcaemic "non-responders" who survived long enough for full study to be made.

The cause of the early deaths in the hypercalcaemic patients who did not show objective responses was mainly the progression of uraemia, leading ultimately to oliguric renal failure. Fortunately, those with a raised blood urea at the time of implantation, who did obtain a good cancer response, may regain a normal blood urea quite rapidly (see case O.Wi., in Appendix, page 579).

Urinary Calcium

Pre-implant urinary calcium levels (Table XIII.II).

In a total of 57 patients, measurements of the urinary calcium had been made during their assessment for pituitary implantation, and at the same time, the presence or absence of skeletal deposits was investigated radiologically. The findings are shown in Table XIII.II.

TABLE XIII.II.

THE FREQUENCY OF RAISED URINARY CALCIUM BEFORE IMPLANTATION IN 57 PATIENTS: CORRELATION WITH BONE METASTASES.

	Numbers of patients					
	Total	Urinary calcium (mEq./24hrs.)				% of patients >15mEq./24hr.
		<10.0	10.0 to 15.0	15.1 to 20.0	>20.0	
Bone deposits	42	16	12	12	2	33% } 26%
No bone deposits	15	13	1	1	0	6% }

It is evident that, with one exception, all patients with calciuria above 15.0 mEq./24hrs. had skeletal metastases recognised radiologically; further, of 28 patients with values over 10mEq./24hrs. 26 had radiological deposits.

Comparison of pre-implant serum calcium and urinary calcium (Fig.XIII.2)

In 57 women being assessed before implantation for breast cancer, (a) at least two consecutive 24-hour urine collections were made for calcium estimation (most being on the standard calcium-restricted diet) and (b) the serum calcium was estimated. The mean values have been taken for plotting in Fig. XIII.2.

There were 13 patients with hypercalcaemia (5.5mEq./l. or higher) of whom seven had a urinary calcium raised to above 15 mEq./24hrs. (11 had a urinary oalcium above 10 mEq./24hrs.) It thus appears that only about half of the patients with an elevated serum calcium also had a clearly abnormal urinary calcium. However, out of seven patients with more substantial elevations of serum calcium to above 6.0 mEq./l., all but one (her blood urea was normal) had hypercalcuria.

There was a total of 15 patients with a urinary calcium above 15 mEq./24hrs; eight* had a normal serum calcium. Thus, hypercalcuria occurred in the absence of a raised serum calcium in about half the cases.

It is clear, therefore, that measurements of urinary calcium cannot be regarded as necessarily reflecting the serum level, when raised values are induced by breast oancer.

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* In six, the ionic concentration of serum calcium was obtained from the Cartesian nomogram of McLean, 1957, according to the total serum protein. In only one was the ionic concentration more than 0.2mEq./l. higher than expected from the total serum calcium, assuming a normal plasma protein of 6.6mg/100ml., and in none was it higher than in four hypercalcaemic normocalcuric patients.

COMPARISON OF URINARY & SERUM CALCIUM IN 57 WOMEN WITH BREAST CANCER BEFORE PITUITARY IMPLANTATION

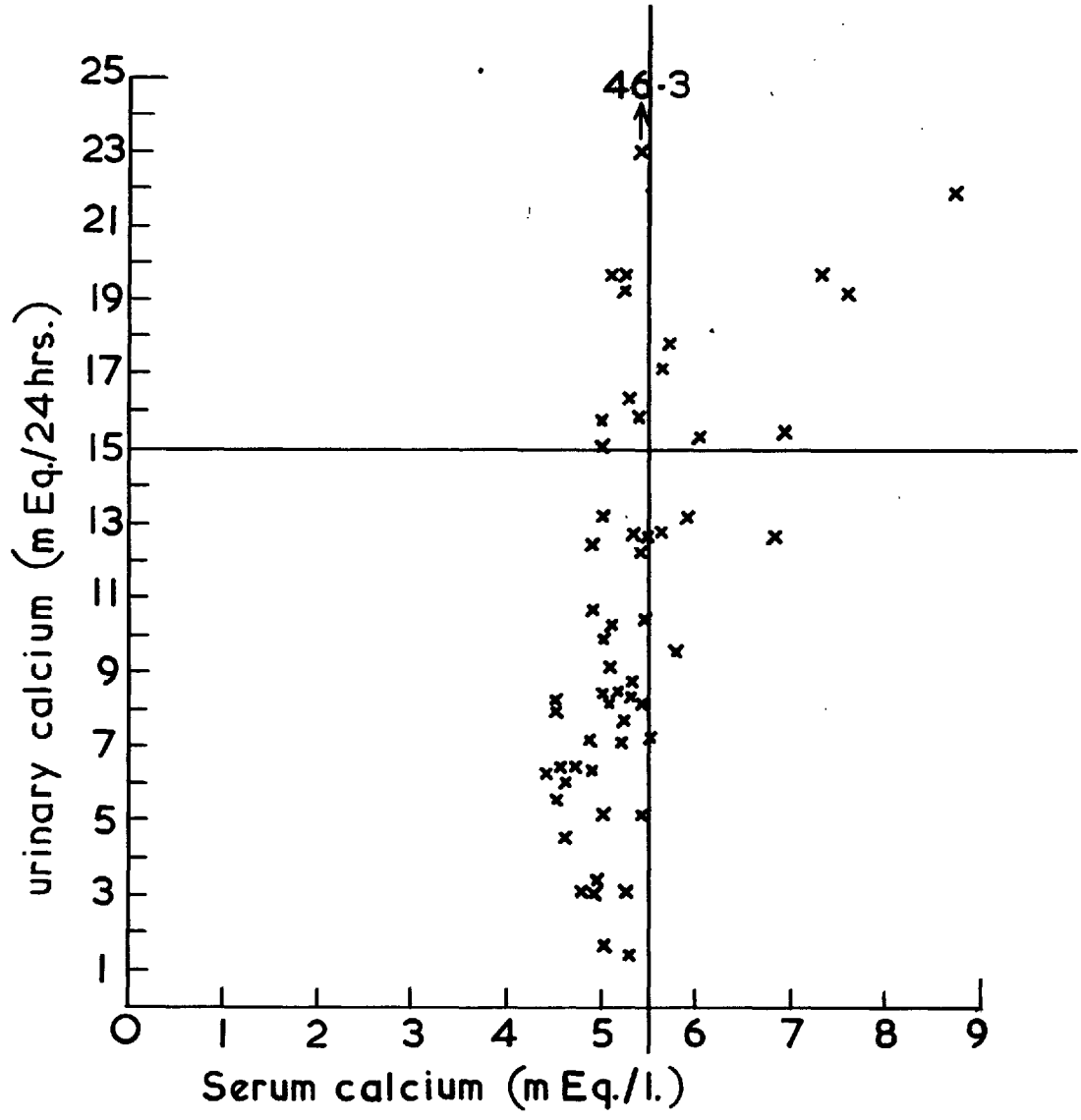


Fig. XIII.2 - Plots are the mean of the urine or serum calcium estimations before the (first) implant. Only cases with two or more urine estimations are shown. The upper limit of normal serum calcium is drawn at 5.5mEq./l., and for urinary calcium at 15 mEq./24hrs.

The effect of pituitary implantation on the urinary calcium excretion (Fig.XIII.3)

A total of 36 patients were followed after pituitary implantation with measurements of urinary calcium, and in addition, their response of the carcinoma assessed objectively. There were 18 "good" responders, 11"mixed" responders, and 7"non-responders". For each patient, in a given phase of cancer activity, the mean of all urinary calcium estimations was taken for plotting. There were usually two or three 24 hour urine collections, but in some cases, up to 11 had been made.

The results are shown in Fig. XIII.3. 23 patients with pre-implant normo-calcuria are shown above, and 13 with hypercalcuria are shown below. It is evident that the only group of patients in which the urinary calcium appears to reflect the objective response of the cancer is the group of 10 initially hypercalcuric "good" responders, and even here, it was only consistently reliable where the pre-implant level exceeded 18 mEq./24hrs. (6 patients). There is almost no agreement between change in urinary calcium and cancer progress in the eight "good" responders and in the six "non-responders" with initial urinary calcium levels below 15 mEq./24hrs.

From these data, it may be said that the urinary calcium was only valid as an index of cancer activity in those cases with really high pre-implant values of at least 18 mEq./24hrs., although a clear fall of over 10 mEq./24hrs., is probably indicative of some cancer remission. An example is described in detail in the Appendix, on page 519, (Case O.Wi.).

The effect of pituitary implantation on the serum inorganic phosphorate

In 33 patients with breast cancer and before implantation, two or more determinations of the serum inorganic phosphorate were made. The mean value was 2.2 mEq./l. (3.7 mg./100ml.) and in 95% cases, the values lay between 1.8 and 2.6 mEq./l. This is almost identical to the normal laboratory range, where 98% of normal subjects lie between

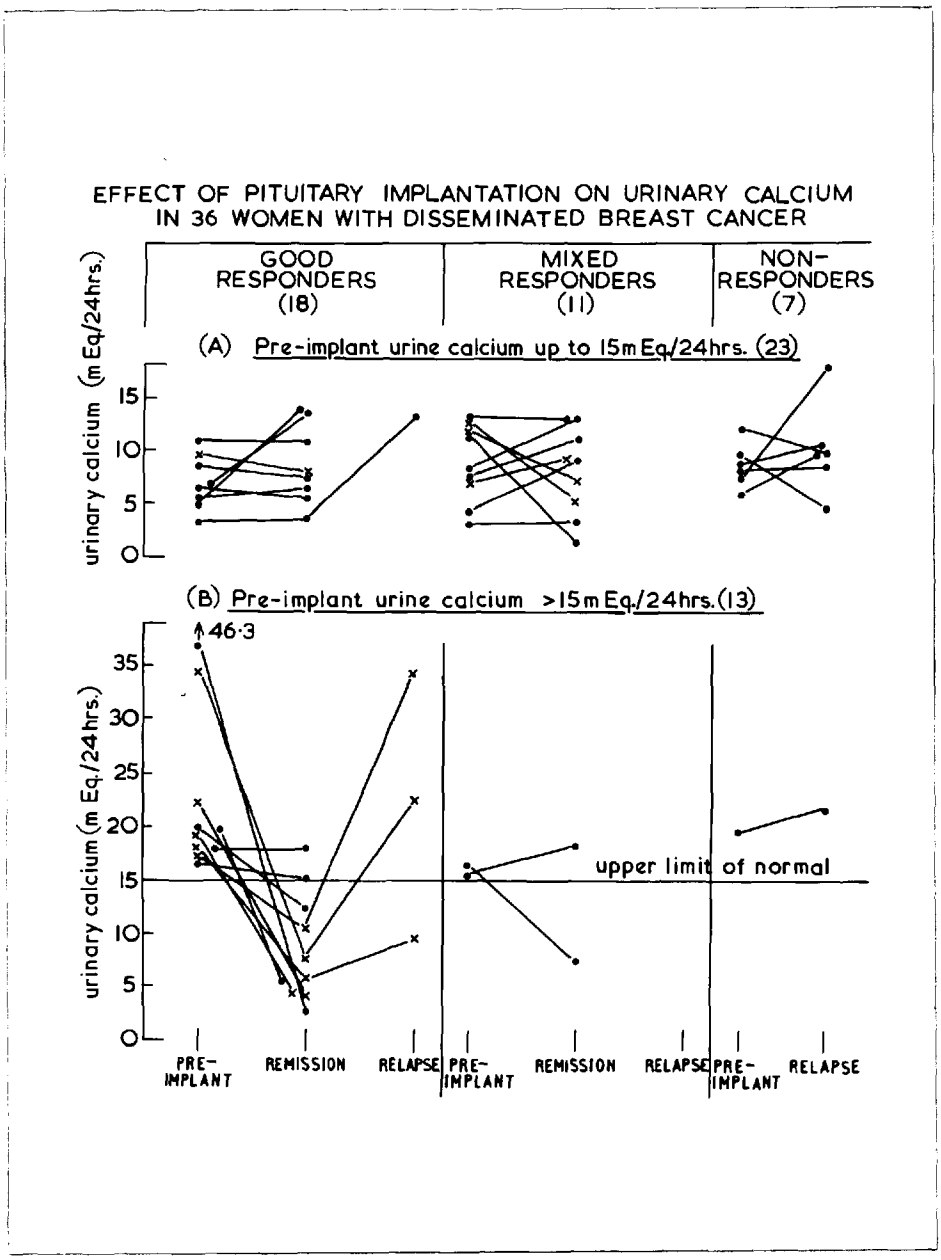


Fig. XIII.3 - Most plots are the means of 2 or 3 collections, but there were up to 11 collections in some. Patients whose pre-implant serum calcium was 5.5mEq./l. or higher are plotted with (x).

1.4 and 2.6 mEq./l. The mean value of the present series of 2.2 mEq./l. is close to the figure 2.1 mEq./l. of Gardner and his colleagues (1962) for normal adult women.

Following implantation, serum inorganic phosphate was measured in most cases on the occasions that the calcium was measured. There were no discernible trends for the values to either rise or fall with cancer remission or advance.

Serum alkaline phosphatase

Serial estimations of the serum alkaline phosphatase were made in 25 patients in whom there was no reason to suspect liver deposits at the time of implantation, and in 15 in whom such involvement was very likely. Only cases in whom the cancer response could be objectively graded were included in the analysis which follows; also, in each oase, the presence (22) or absence (3) of bone deposits, and their predominant character (osteolytic or osteoblastic) was ascertained. Where patients had more than one implant, each was regarded as a separate case.

The results have been plotted in Fig. XIII.4 a, b, and c. There is no difference between the patients shown in these three figures; they are shown as three figures purely because greater numbers cannot be plotted on a single graph. The analysis of these data will now be given under relevant headings.

The time of the peak in the post-implant rise.

To examine this point, patients from Fig. XIII.4 were selected whose pre-implant value was not substantially raised, who showed a definite peak and a subsequent fall. In this way, a rise from progressing unsuspected liver involvement could be excluded. Arbitrarily, criteria were fixed so as to require the mean pre-implant value to be under 20 K.A. units, the peak to be above 30 KA.units, and the subsequent fall to be below 20 KA.units by the 120th. day.

There were six patients in Fig. XIII.4 who met these criteria (with one minor exception). The peak value of alkaline phosphatase

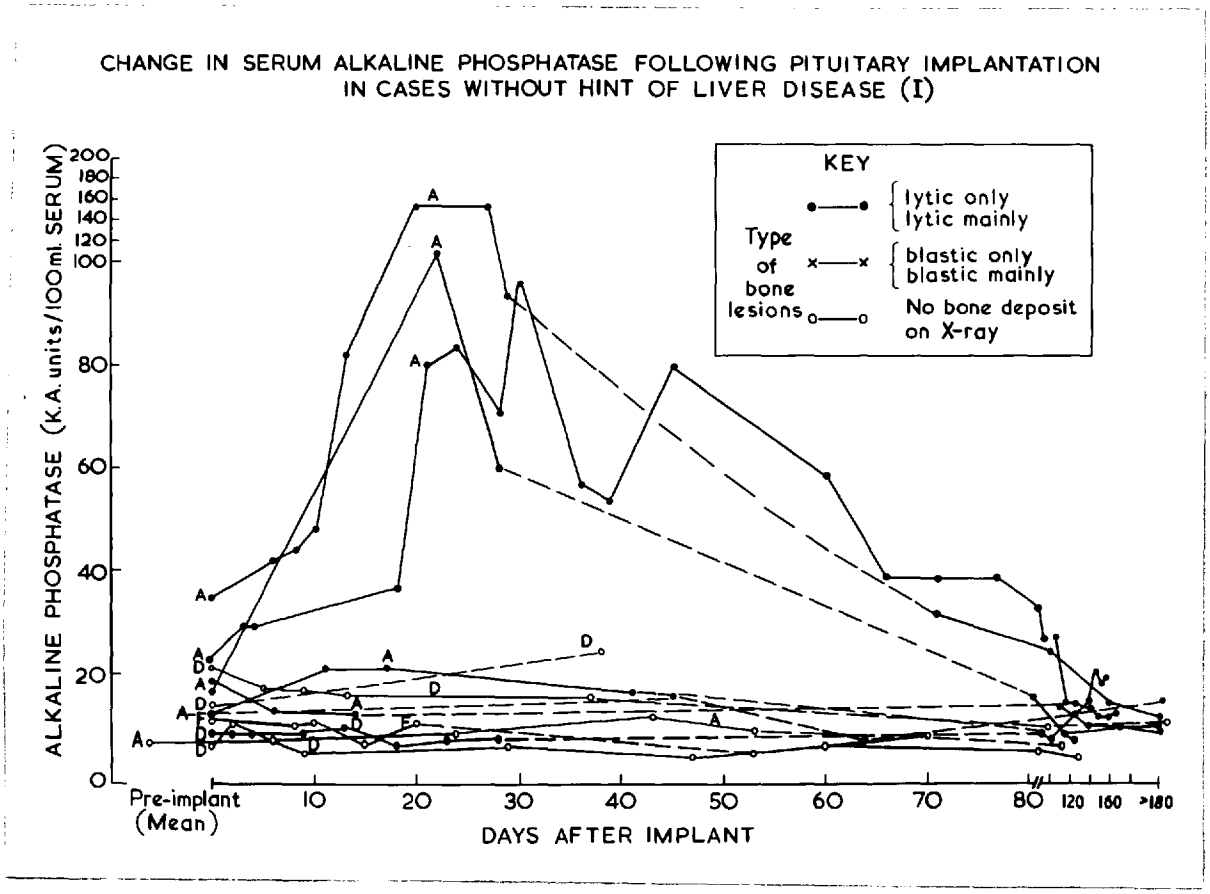


Fig. XIII.4a - Patients' response to implant was graded from A to F, and these letters are shown alongside their serial plots. The data from all the patients without liver disease that were studied are shown in Figs. XIII.4a, b, and c. (see next pp).

CHANGE IN SERUM ALKALINE PHOSPHATASE FOLLOWING PITUITARY IMPLANTATION IN CASES WITHOUT HINT OF LIVER DISEASE (II)

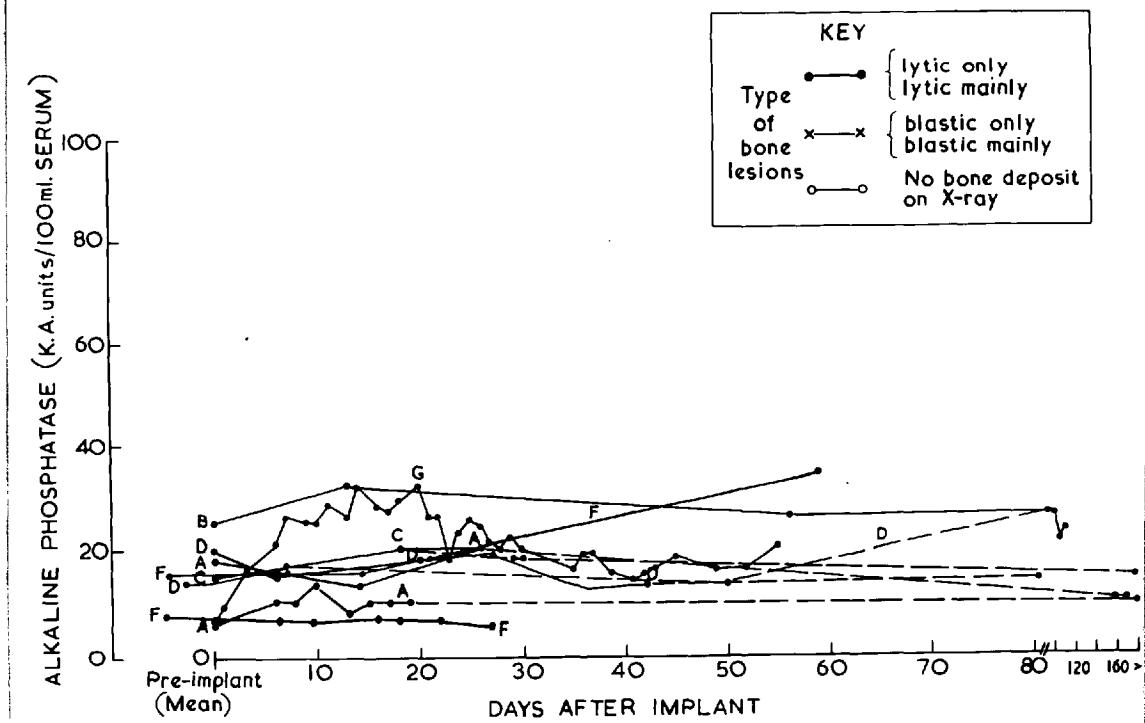


Fig. XIII.4b

CHANGE IN SERUM ALKALINE PHOSPHATASE FOLLOWING PITUITARY IMPLANTATION IN CASES WITHOUT HINT OF LIVER DISEASE (III)

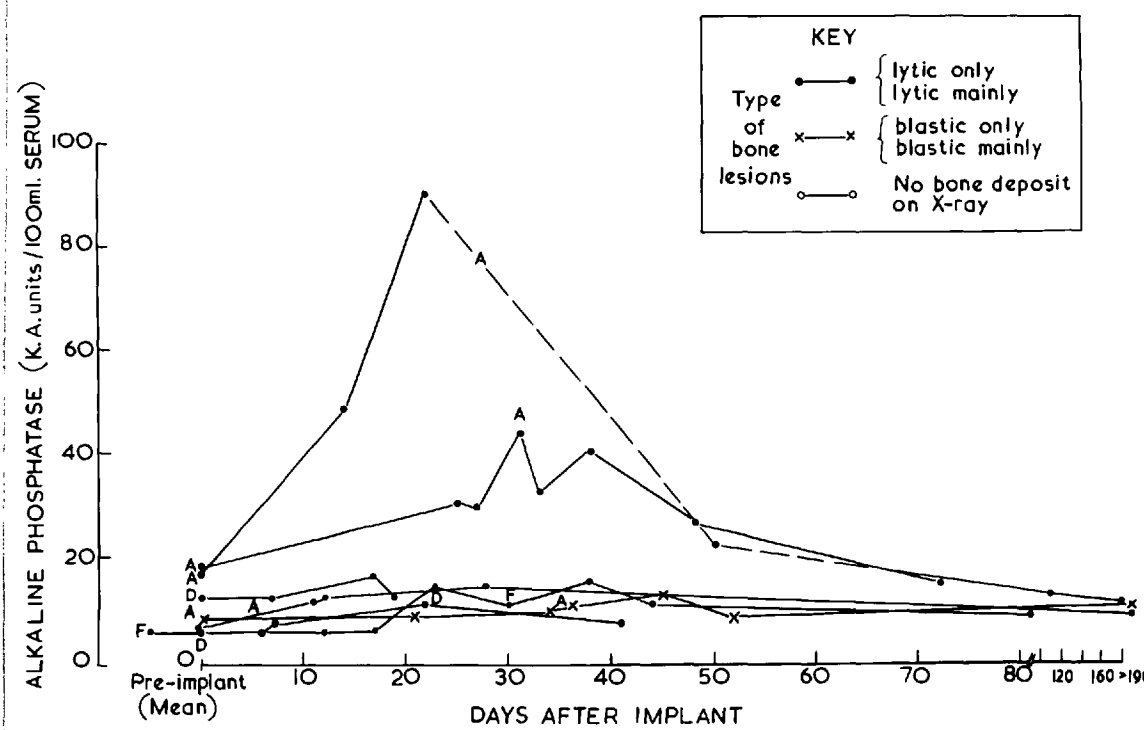


Fig. XIII.4c.

could have lain between day 14 and day 38, and in fact, all peaks actually recorded lay between day 14 and day 31.

The duration of the post-implant rise.

Five of the above patients with a pre-implant value under 20 KA. units had a serum alkaline phosphatase above 30 KA. units lasting from the 14th to 38th days, quoting the narrowest possible range, or from the 13th to 50th day, quoting the widest possible range (the patient who had sustained a fractured femur and concomitant peak in alkaline phosphatase was not considered after this event).

Defining the level to which the alkaline phosphatase peak must rise to be significant of cancer healing.

For this purpose, out of the population of Fig. XIII.4 where there was no suspicion of liver disease, those with grade A objective responses were compared with those with grade F responses, i.e. those with the best response and those with no discernible cancer effect. The highest value achieved by the group of four non-responders between days 14 and 31 was 18 KA units, and even this case was in fact showing a steady trend upwards towards death, possibly therefore due to liver involvement. In contrast, among the 11 grade A responders, 8 showed peaks above 18 KA units, and 6 rose to above 30 KA units. None of the 8 cases with a grade D response showed a peak above 18 KA units.

It would therefore appear that a patient showing a post-implant peak of over 30 KA units, occurring between day 14 and 31 and falling to under 20 KA units (by day 120), is with a high probability going to enjoy a substantial cancer remission.

The effect of hepatic involvement on the post-implant trend of the serum alkaline phosphatase. (Fig. XIII.5 a and b).

There were 15 patients who very probably had hepatic involvement at the time of implantation. Their serial post-implant serum alkaline phosphatase figures are plotted in Fig. XIII 5 a and b.

To ascertain the effect of liver disease itself, the five patients

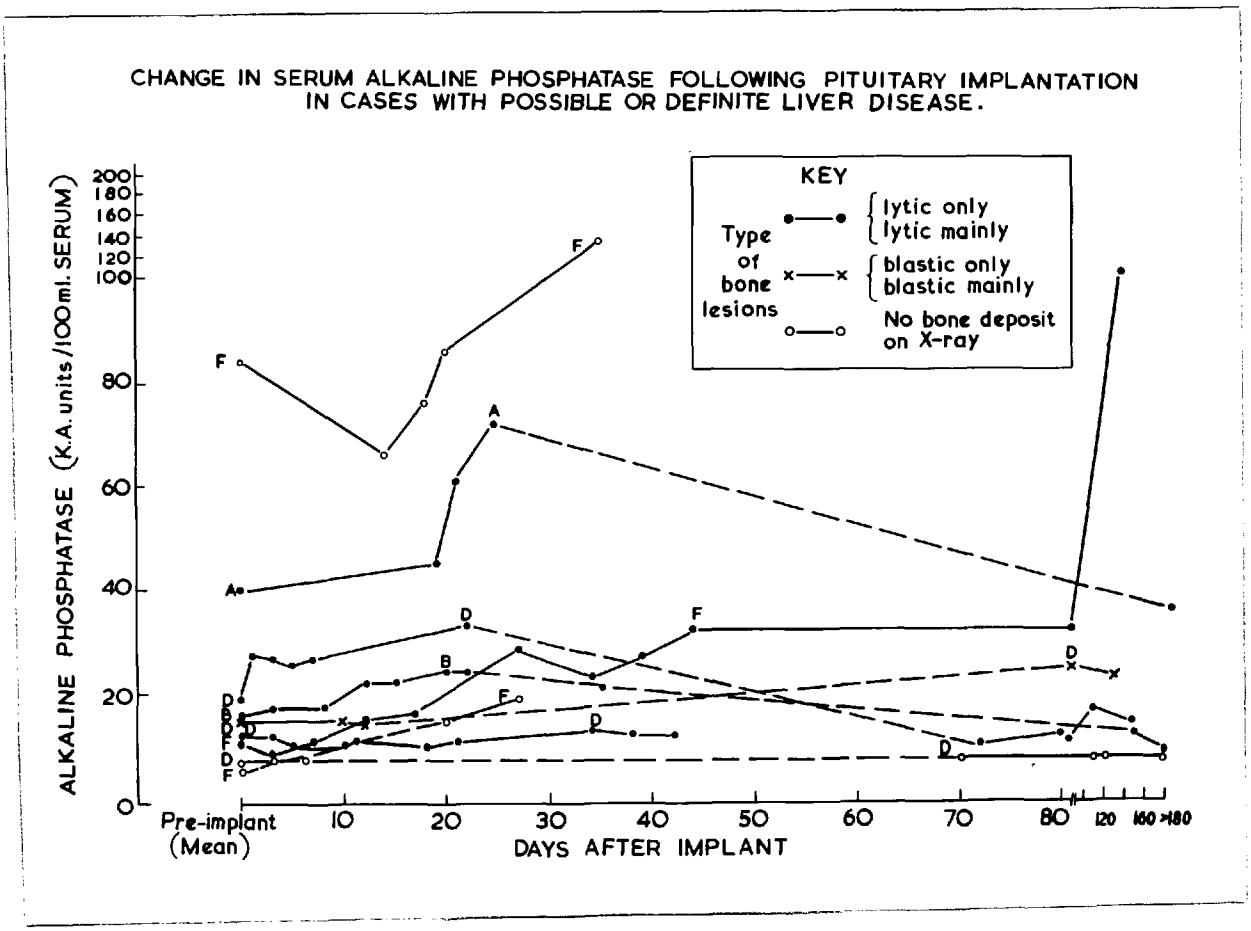


Fig. XIII.5a - Patients' response to implant was graded from A to F, and these letters are shown alongside their serial plots. The data from all the patients with possible or definite liver disease are shown in Figs. XIII.5a and b.**(see next p.)**

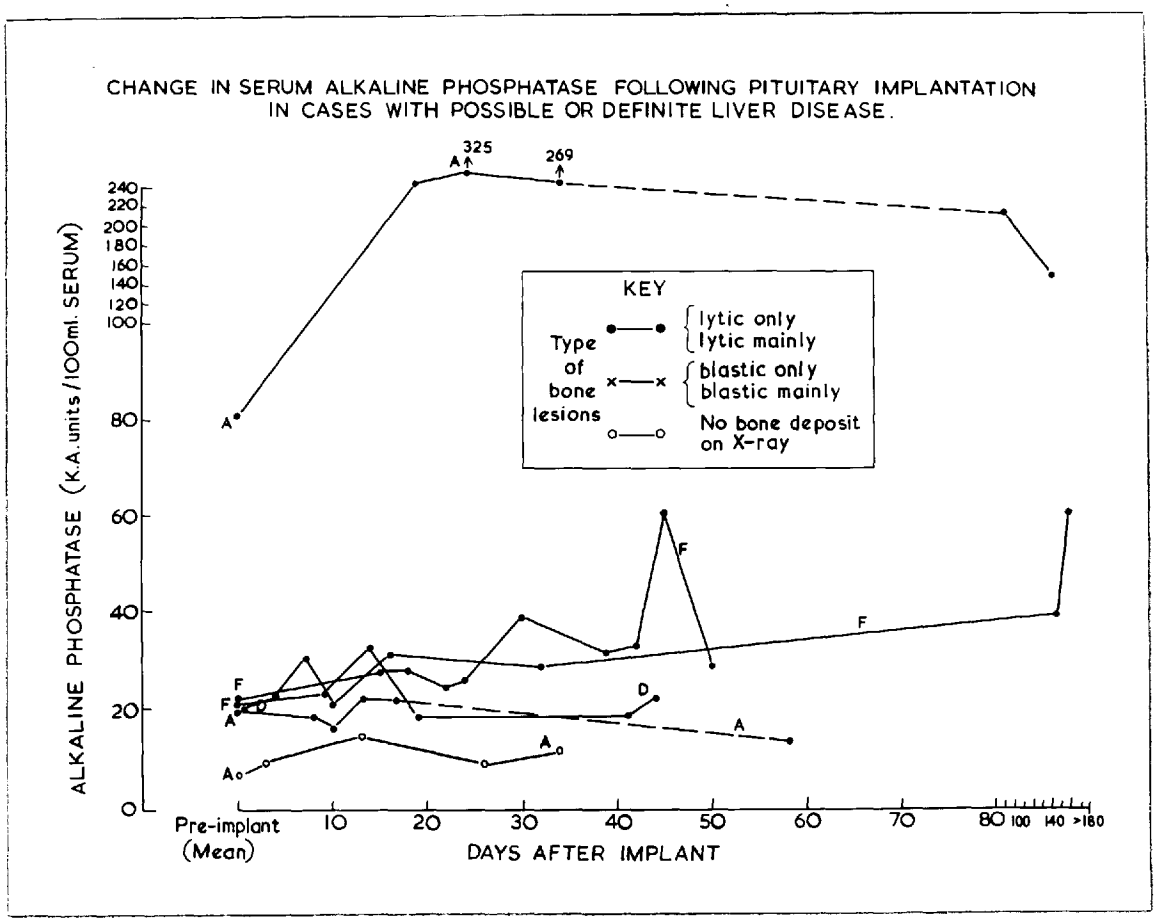

CHANGE IN SERUM ALKALINE PHOSPHATASE FOLLOWING PITUITARY IMPLANTATION
IN CASES WITH POSSIBLE OR DEFINITE LIVER DISEASE.
ALKALINE PHOSPHATASE (K.A.units/100ml. SERUM)
240
220
200
180
160
140
120
100
80
60
40
20
0
325
269
KEY
Type of bone lesions
lytic only
lytic mainly
blastic only
blastic mainly
No bone deposit on X-ray
Pre-implant (Mean)
10
20
30
40
50
60
70
80
100
140
>180
DAYS AFTER IMPLANT

Fig. XVIII.5b.

with a grade F cancer response can be examined, in that no rise in alkaline phosphatase would be expected from cancer regression. Among the five patients, three did in fact have a value of over 30 KA. units between day 14 and day 31; however, none showed a subsequent fall, but continued to rise. They would not therefore have qualified as showing a significant "peak".

To ascertain the combined effect of cancer regression and liver disease, the ten patients with a grade A, B or D response can be considered. Four showed a value of over 30 KA. units between day 14 and 31, so in them the possibility of either cancer regression or liver disease or both, is raised. If the above-determined criteria are applied to their serial values, it is found that all showed a fall in level after day 31, and had shown an initial rise when compared with the pre-implant level. Hence, it would be reasonable to attribute such a peak-effect to bone healing. On the other hand, two of them had pre-implant values above 20 KA. units and neither fell to below this, so it would be probable from the alkaline phosphatase data alone that these two also had liver disease.

Definition of a significant "peak-effect" of the serum alkaline phosphatase.

From the data thus far presented, it is possible to define the criteria for inferring cancer healing from the serial alkaline phosphatase.

a. A peak value of above 30 KA. units, occurring between day 14 and 31.
b. A pre-implant level of under 20 KA. units, and the peak falling to this level by day 120.
c. Where the pre-implant level is above 20 KA. units, a clear rise and fall with a peak above 30 KA. units between day 14 and 31, probably indicates both healing cancer and liver involvement (in the absence of healing fractures).

Testing the whole series for a "peak-effect" in serum alkaline phosphatase

There are a total of 40 patients whose serial data are shown in Figs. XIII.4 and XIII.5. In all, the trend as far as day 31 is clear. There were 10 with a significant "peak-effect", of whom eight were

grade A and two were grade D responders; four of them probably also had liver disease (on other criteria).

The time after implantation for significant change to occur in the serum and urinary calcium and serum alkaline phosphatase. (Table XIII.III.)

One or more of these parameters of calcium metabolism which showed a post-implant change were followed serially after implantation in 25 different patients, thus enabling the date of any change resulting from implantation to be ascertained.

The results are shown in Table XIII.III with the criteria used for a significant change in the footnote. It is evident that a significant fall in serum calcium and rise in alkaline phosphatase can occur by the third day, and a fall in urine calcium by the eighth day. In most cases, if a change in any of the three parameters was to occur, it did so by the 14th day.

TABLE XIII.III

TIME FROM IMPLANTATION FOR SIGNIFICANT CHANGE* TO OCCUR IN SERUM AND URINARY CALCIUM AND SERUM ALKALINE PHOSPHATASE

	No. Patients	No. days for change to occur in individual patients	Narrowest range of times for change (days)
Serum calcium	11	2,3,4,5,5,6,8,9, 11,13, 19.	2 to 11
Urine calcium	8	8,8,11, 15, 18, 19 26, 28.	8 to 11
Serum alk. phosphatase	10	3, 6,7,7,10, 13, 14 21, 22, 25.	3 to 21

* significant change:
serum calcium - a fall of > 0.5mEq./l. from an initial abnormal value
urine calcium - a fall of > 5mEq./24hrs. from an initial abnormal value
serum alkaline phosphatase - a rise to above 20 KA. units from an initial normal level, or by over 5 KA. units from an initial high value.

Correlation between the serum total acid phosphatase and (a) the serum calcium and (b) the urine calcium (Figs. XIII.6 and XIII.7.)

This was investigated in view of two findings. Firstly in Chapter XIV (page 374) it is shown that the serum total acid phosphatase (TAP) level approximately parallelled the extent of bone metastases, and was only elevated in the presence of bone involvement. Secondly, it has been already shown in the present chapter that an elevated serum and urine calcium was virtually confined to patients with radiological bone deposits.

In Fig. XIII.6 is shown the TAP and serum calcium data from 36 patients before implantation, irrespective of the number of pre-implant observations from which mean values were derived. There is a hint of a correlation evident on inspection. When the 11 hypercalcaemic patients are considered, it is found that eight had an elevated TAP (one of the three discordant cases had a high and a normal pre-implant TAP, yielding a mean level of 3.0 K.A. units/100ml.). On the other hand, out of 25 patients with a normal serum calcium, only 13 had an elevated TAP.

In Fig. XIII.7 is shown the data correlating TAP and urinary calcium from every untreated patient with two or more pre-implant urine estimations. Here there is an obvious correlation evident. For instance, all but 2 of the 19 patients with an elevated TAP had a urinary calcium above 10 mEq./l, and 12 had a urinary calcium that was clearly high. On the other hand, out of 10 patients with a normal TAP, 7 had a urinary calcium under 10 mEq./24hrs. The converse holds nearly as well, in that out of 21 patients with probable hypercalciuria, 17 had a raised TAP, and out of 14 patients with clearly manifest hypercalcuria, 12 had raised TAP.

CORRELATION OF PRE-IMPLANT TOTAL ACID PHOSPHATASE WITH SERUM CALCIUM IN 36 PATIENTS WITH DISSEMINATED BREAST CANCER

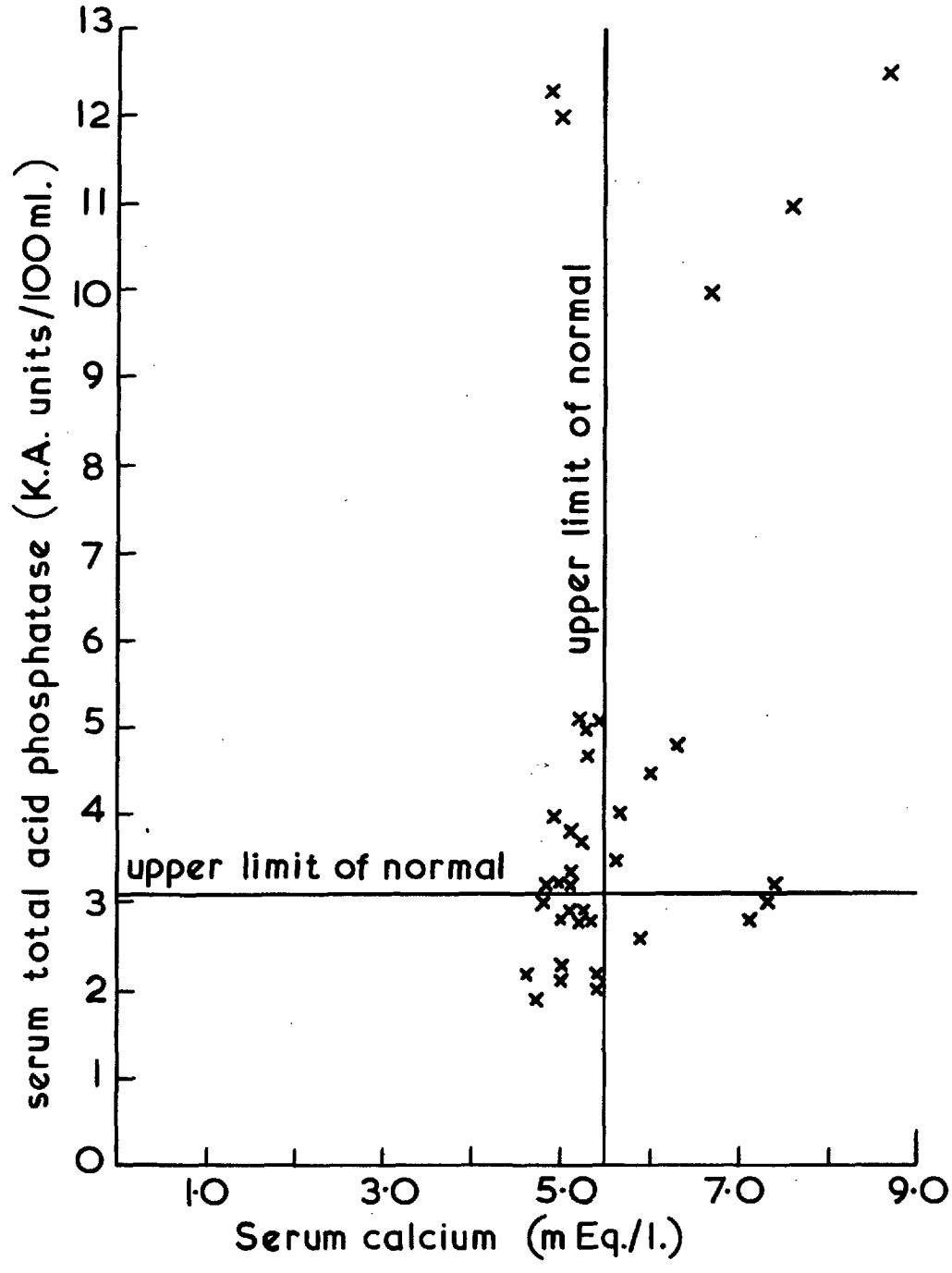


Fig. XIII.6 - In most patients, values are the mean of several estimations.

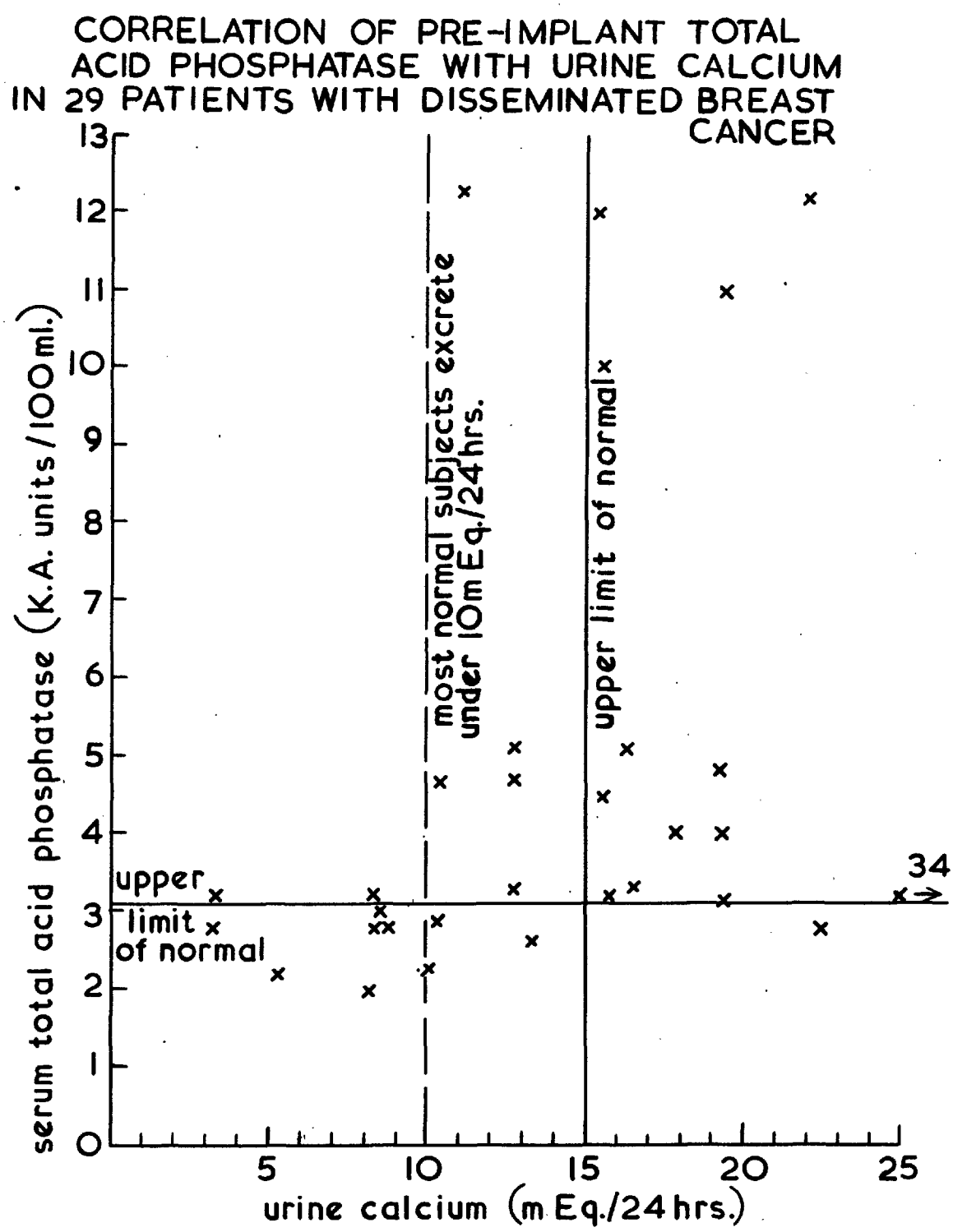


Fig. XIII.7 - In all cases, the urine value is the mean of more than one collection.

DISCUSSION

Serum Calcium

It is well known that a proportion of patients with disseminated cancer show an elevated serum calcium; bone metastases have usually been present, but not always (e.g. Plimpton and Gellhorn, 1956). With cancer of the breast, hypercalcaemia is not at all uncommon. In the present study, 21% of patients (13 of 63) had raised mean pre-implant values; all had skeletal metastases. This is similar to the incidence of 30% (of 157 cases coming to adrenalectomy) found by Hellstrom and Franksson (1958) and 29% quoted by Myers (1960). 14% of 71 patients with osteolytic metastases in the series of Swyer et al. (1950) had hypercalcaemia.

One explanation that has been offered (Albright and Reifenstein, 1948) is that the raised serum calcium is caused by "osteolysis" due to expanding bone secondaries, but this can hardly account for the cases without bone involvement, nor does it allow for the frequent finding of a normal serum calcium in the presence of massive skeletal involvement. Perhaps the explanation in some cases (as postulated by Albright and Reifenstein, 1948) lies in the secretion of a humoral substance by the cancer. Recently, Lemon (1962) found a high serum parathormone-like activity (and hypercitraemia) in the serum of three such hypercalcaemic women with breast cancer. Gardner and his colleagues (1962) also postulated the secretion of osteolytic material by the cancer; they showed that the rise in serum calcium occurred in spite of a fall in tubular reabsorption of calcium, and unchanged tubular reabsorption of phosphate and that an implant of breast cancer against rat calvarium causes osteolysis (Gordan et al., 1962).

It is apparent that in a patient with hypercalcaemia, a fall to normal of the serum calcium after pituitary implantation is good evidence of cancer healing, as 8 out of the 10 who did so showed a grade A response of their disease. The 3 implants that did not reduce a raised serum calcium were soon followed by death from the inevitable uraemia and so their cancer response could not be independently assessed by the usual radiological and clinical criteria. In addition to being a

reliable index of cancer response, a fall in serum calcium is an early indication of a cancer response. Some patients show a fall as early as the third day, and most who will ultimately show an alteration in serum calcium will do so by the 14th day. Similar early changes also occur with hypercalcuria, and serum alkaline phosphatase. This is well before any radiological or objective clinical change is established.

It would appear that in routine clinical practice, it is only worthwhile following the serum calcium after implantation, if the pre-implant value is raised. There was no example of a patient showing a rise for the first time after implantation; this suggests that the factor which determines such an elevation is usually present by the time dissemination of the cancer has occurred. The frequency of post-implant measurements which can be recommended from consideration of the material in this chapter, would be twice-weekly for the first two weeks, and then weekly until normal. After this, it can be followed on a three-monthly basis to give what is probably the first indication of cancer relapse.

Urinary calcium

Change in the urinary calcium has been widely considered to be a significant parameter of breast cancer progress (e.g. Laszlo et al., 1952; Pearson et al., 1954; Gerbrandy-Hellendorn, 1957; Strong and Stokoe, 1957), although this has been questioned by Gardner and Gordan (1962). In the present study it was found, as with the serum calcium, that clearly elevated levels (above 15 mEq./24hrs.) were virtually (14 out of 15 cases) confined to patients with radiologically evident bone deposits. The overall frequency of hypercalcuria before implantation was 26%; this is comparable to the figure of 34% of 166 patients quoted by Hellstrom and Frsnksson (1958). Gerbrandy and Hellendorn (1957) found that 18% of 115 patients excreted over 15 mEq./24hrs.; all such patients had osteolytic deposits, and the extent of the bone involvement was reflected by the urinary calcium. A change in urinary calcium after implantation was almost confined to those with high pre-implant excretions (Fig.XIII.3). For instance,

there was not a single fall after implantation among eight good responders whose pre-implant level was under 15 mEq./24hrs., whereas eight out of ten good responders with pre-implant levels that were above this level, showed substantial falls into the normal range. The effect, if any, of the post-implant maintenance cortisone per se would be to increase the urinary calcium, as a consequence of a decrease in the tubular reabsorption (Gardner et al., 1962). As with the serum calcium, no instance of acquired hypercalcuria was found following implantation, again suggesting that the factor responsible is at a significant level at the time dissemination first occurs. Hence, there is little to be gained by following the urinary calcium if the pre-implant level is under 15 mEq./24hrs.

From the practical point of view, there would seem to be little justification in following the urinary calcium, as the discovery of the minority of patients with high pre-implant values entails timed urine collections of all patients on a standard diet during the pre-implant assessment, while post-operatively it can be followed only on an in-patient basis; furthermore, at least half of the hypercalouric patients also have hypercalcaemia, and this can be more readily followed, and shows less fluctuation and is of undoubted specificity.

A most interesting theoretical consideration is raised by the comparison of the pre-implant serum and urinary calcium levels. About half the patients with a raised serum calcium also had a raised urinary calcium, and about half the patients with a raised urinary calcium, also had a raised serum calcium. The hypercalcuric patients who have a raised serum calcium can be readily understood if it is postulated that there is a factor, arising when there are metastases in bone (mainly), which has a hypercalcaemic action. But the perplexing group are the hypercalcuric patients who had a normal serum calcium. Hellstrom and Franksson (1958) found 25 such cases. There were eight in the present study and it so happened that six were good responders. When the post-implant urinary calcium excretions were followed, three showed striking falls into the normal range.

There can be no doubt in these three patients therefore, that there was a very potent factor responsible for their intense hypercalcuria, arising as a result of disseminated breast cancer, which was mainly in bone; it had no significant hypercalcaemic effect, and fell during cancer remission. It would be of great interest to compare the biological activity of this factor with parathormone activity, [illegible], and to obtain autopsy examination of the parathyroids. Further support for a close relationship between the presence of bone metastases and an elevated urine calcium (and to a lesser extent with serum calcium) is provided by the correlation between the serum total acid phosphatase (TAP) and calcium levels. That TAP elevation reflects bone metastases is clearly shown in Chapter XIV, page 368

Consideration of the data of the present study provides an explanation of the failure of Gardner and Gordan (1962) to discover any agreement between the urinary calcium excretion and breast cancer activity. They came to this negative conclusion when they found that the mean urinary calcium excretion of a group of patients whose cancer was advancing was found to be similar to the mean of a group of patients whose cancer was remitting on androgens or prednisone plus triiodothyronine, after having excluded from the study those patients who had severe hypercalcaemia. It is evident that as hypercalcuria without hypercalcaemia is unusual anyway, the urinary calcium values of the few hypercalcuric normocalcaemic patients who might have remitted from their hormone therapy, would be obscured when added to a number of other initially non-hypercalcuric patients who would have shown no fall. The rarity of hypercalcuria could also explain their finding that the mean urinary calcium of 26 patients with bone lesions was not significantly higher than that of 25 patients without bone lesions. Their further finding that patients with advancing disease did not show increasing calcuria could be explained by their patients being rather advanced in their disease when entering their hormone trial, and hence, on the data of the present study, having virtually maximal calcuria when the first measurement was made. Only one of nine non-responders of the present study showed an increase in serial

urinary calcium excretions after implantation. On the other hand, their own data shows that their two patients with initial urinary calciums of over about 15 mEq./l., and who did respond to hormone therapy, showed large falls when their osteolytic lesions regressed.

Serum inorganic phosphate

The serum inorganic phosphate level has not been frequently investigated in breast cancer. This is reviewed by Gardner and his colleagues (1962), who found significantly higher levels in a group of untreated patients than in a group responding to androgen therapy and a group of normal women. The difference was small, and so the pre-implant levels found in the present study cannot be evaluated by merely comparing their mean level with those reported elsewhere; a simultaneous series of measurements would have been required from a group of normal women. However, the mean value of the 33 untreated cases of breast cancer was 3.7 mg./100ml., which is similar to the figure of 3.5mg./100ml. these authors quote for normal women; no trend downwards was observed when patients went into remission. Neither were there any patients with a subnormal level, which is rather against any hypothesis suggesting that the neoplasm secrete typical parathormone which leads to the high serum calcium found in some cases of advanced cancer; however, hypophosphataemia has been clearly described (e.g. Plimpton and Gelfhorn, 1956).

Serum alkaline phosphatase

The criteria for the use of serial measurements of the serum alkaline phosphatase for following healing of bone deposits has not been examined hitherto in detail. Huseby (1955) found that it was useful in following the response to testosterone propionate, and Pearson (1957) in assessing response to endocrine extirpation. The points to be considered are the definition of a significant elevation, and avoidance of erroneously ascribing to bone healing an elevation due to progressing liver deposits. It was found in the present study that if a rise to about 30 KA. units occurred, with a peak between day 14 and day 31, and was back to under 20 KA. units by day 120, the patient would experience a cancer regression, usually of grade A. If the pre-implant value was above 20 KA units, probably due to liver

disease, a clear "peak-effect" with peak between day 14 and day 31 was still indicative of bone healing. A significant post-implant "peak-effect" was confined to patients with radiologically evident bone deposits. The alkaline phosphatase thus is shown to be a most reliable method of showing cancer healing. Presumably it reflects osteoblastic activity in initiating repair of osseous lesions. Less specificity in the "alkaline phosphatase flare" was found by Woodard et al. (1954), in reporting on the effect of hormone therapy on breast cancer. It should be done weekly from the time of implantation to day 35 (so as to embrace the period of the "peak-effect"), and then every few weeks up to the 18th week, to show that it returns to the pre-implant level. There is no rise terminally.

SUMMARY

1. In 63 patients with disseminated breast cancer, the serum calcium was measured and a radiological skeletal survey was made before implantation. 13 patients (21%) showed a raised mean serum calcium of 5.5mEq./1.or higher, and all of these patients had radiologically evident bone deposits. None of the 17 patients without bone lesions had a raised value.

2. Serial serum calcium measurements were made after implantation in 40 patients in whom the cancer response could be assessed on other criteria. The only group of patients showing a clear fall after implantation were the group of eight who both had a raised pre-implant level, and a good cancer response. There was no trend for initially normocalcaemic patients to show falls during a good response to implant, or a rise in the absence of any cancer response. A terminal rise was seen in all four good responders who had obtained a normal serum calcium during cancer remission.

3. In 57 untreated patients with disseminated cancer, both the urinary calcium was measured and a radiological skeletal survey were made. Definitely raised excretions of over 15 mEq./24hrs. were found in 15 patients (26%), and in 14 there were radiologically evident bone deposits. A value of over 10 mEq./24hrs. was found in 28 patients, and all but two had bone metastases visible.

4. Serial measurements of urinary calcium were made in 36 patients whose cancer response was independently assessed. The only group of patients showing a clear fall in urine calcium after implantation was the group of 10 with initial hypercalcuria, and good responses. Eight showed falls to normal, and all three followed to death showed terminal rises. There was no trend for the urinary calcium to fall with cancer regression in the eight patients with an initial normal urine calcium excretion, nor did values tend to rise in normocalcuric patients (one exception) in the absence of cancer response.

5. Both serum and urine calciums were measured in 57 patients before implantation. About half of the patients with a serum calcium of 5.5mEq./l. or above, had a urine calcium of 15 mEq./l. or above. Similarly, about half the patients with hypercalcuria also had hypercalcaemia.

6. There were eight patients with a pre-implant urinary calcium of over 15 mEq./l., but normal serum calcium levels, and whose post-implant cancer response was independently ascertained. Three showed substantial falls of urine calcium excretions into the normal range, during cancer remission.

7. It is postulated that there is both a hypercalcaemia-inducing factor, and sometimes independently, a hypercalcuria-inducing factor, elaborated in a proportion of women with breast cancer. Both factors reach significant levels by the time metastatic spread has occurred, and are readily reduced if there is a good response of the cancer shown on other grounds, only to reappear during terminal relapse. About half the patients possess both factors, and the other half have but one or the other in significant amount. The factors are both closely, although not exclusively, related to the presence of bone deposits, as shown both radiologically and by the serum total acid phosphatase level.

8. Serial measurements of the serum alkaline phosphatase were shown to be a reliable means of following breast cancer healing. Criteria for a significant response were that in those with pre-implant values below 20 KA. units, a peak value of over 30 KA. units should be reached between the 14th and 31st post-implant days, and that the levels should fall to under 20 KA. units by the 120th day; in those with initial pre-implant values above 20 KA. units, a clear rise and fall, with peak between the 14th and 31st days is probably indicative of cancer regression in the presence of liver disease.

9. 40 patients were followed with serial measurements of serum alkaline phosphatase after implantation, and the general cancer response assessed. There were 10 patients who met the criteria stated in paragraph 8 above; in 8 there was a "good" and in two there was a "mixed" cancer response; all had bone deposits.

10. Change in the serum and urinary calcium and alkaline phosphatase began between the 3rd and 21st post-implant day, and in most cases, by the 14th day.

11. It is considered that the serum calcium is a valuable index of cancer activity in those with a pre-implant value of 5.5 mEq./l. or above, and should be followed both as an early indication of cancer remission, and as a sign of terminal relapse. Serial observations of urinary calcium are not recommended, as it is a troublesome measurement to take, and in but rare instances does it provide information which is not given by serum measurements. Serial measurements of the serum alkaline phosphatase is recommended during the first five weeks; it should be further followed if a rise had occurred.

(2)

CHAPTER XIV

THE EFFECT OF PITUITARY IMPLANTATION ON SERUM TOTAL ACID PHOSPHATASE AND SOME GLYCOLYTIC ENZYMES IN PATIENTS WITH DISSEMINATED BREAST CANCER. CORRELATION OF ENZYME LEVELS WITH SITE OF METASTASES.

The principle of following the level of serum enzymes is well established as a means of following the response to therapy of carcinoma of the prostate. No such enzyme estimation has been generally used for breast cancer. This is particularly unfortunate, because the management of disseminated breast cancer involves a series of hormone administrations and endocrine ablations, each more hazardous than the last; yet the decision to proceed with further endocrine manipulations is largely based on the response to the previous treatment, and it is here that more parameters of cancer activity are needed. While it is usually possible to assess the response to an endocrine manipulation by clinical or radiological means, or by following the serum and urinary calcium and serum alkaline phosphatase (Chapter XIII), there remains a proportion of patients in whom none of these parameters are appropriate, and the clinician must then decide upon further therapy with incomplete knowledge, or wait until obvious clinical deterioration occurs. There is thus an urgent requirement for further parameters of breast cancer activity.

That serum glycolytic enzyme determinations might provide an index of cancer activity had been suggested by the classical experiments of Warburg and Christian in 1943. They noted an elevation in serum aldolase in rats with large tumours. Sibley and Lehninger (1949b) found raised aldolase values in 20% of 104 patients with cancer, while

they noted falls in rats when tumours were surgically removed. Hill and Levi (1954) and White (1958) found raised serum lactic dehydrogenase (LDH) in most patients with cancer.

Bodansky (1954) and Myers and Bodansky (1957) showed some correlation between serum phosphoglucose isomerase (PGI), and remission of bone and liver deposits, and urine calcium, in breast cancer treated by testosterone and endocrine ablation. Lemon and Reynolds (1956) showed a correlation between serum copper-resistant acid phosphatase and regression of bone metastases in breast cancer treated with cortisone. Copper-resistant acid phosphatase was shown by Abul-Fadl and King (1949) to be similar to the formol-stable fraction (FSAP).

No author hitherto has showed a correlation between the various enzymes and site of metastases, beyond the data of Bodansky (1957b) which suggested that a high ratio of serum phosphoglucose isomerase: phosphoglucomutase favoured bone deposits, whereas a low ratio favoured liver deposits.

The present study was undertaken with a view to testing a number of serum enzymes, by following serial levels in cases of metastatic breast cancer treated by pituitary ablation. In this way, their reliability in indicating the site~~of~~presence of disseminated cancer, and showing cancer progress could be assessed. Data were obtained for TAP (total acid phosphatase), PGI (phosphoglucose isomerase), PGM (phosphogluconatase), aldolase, 5-N (5-nucleotidase). The work was made possible by the generous co-operation of Dr. K.A. Jegatheesan, and later, Dr. D.M. Campbell, research biochemists in enzymology, who did all the enzyme determinations personally.

PLAN OF CLINICAL STUDY

Patients studied

Thirty women with disseminated breast cancer who were treated by pituitary implantation, were followed for up to 3½ years. The duration of follow-up will be given with the results of each data analysis. Serum estimations were carried out from March 1958 to January 1962 .

Method of study

For each patient, there is a pre-implant phase, and then either "remission" followed by a "relapse" phase (if there was any cancer response), or just a "post-ablation" phase (i.e. no cancer response). For each patient, during each phase the mean of all determinations of each enzyme was calculated, and it is this value (with number of determinations) which will be plotted in the results section. In general, it was found that unless at least three determinations could be made in a given cancer response phase, an enzyme assessment might not be valid, owing to day to day fluctuations.

Blood for serum enzyme levels was taken as frequently as possible, from the time each patient was first seen for consideration of pituitary implantation up to the last out-patient visit before death. On each specimen as many different enzymes were measured as opportunity allowed, but as soon as it appeared that TAP and PGI might be especially useful, these two enzymes were always done. It was usually possible to obtain three sera before implantation, and then every few days for the following three weeks in hospital. Thereafter, sera were taken at out-patient visits and admissions for reassessment, giving an average of one measurement monthly, up to death.

Cancer response was graded, using all available criteria other than enzyme data, into Grades A to F, and thereby into "responders", "mixed-responders", and "non-responders" as defined in Chapter XII. For each patient in the groups of "responders" and "mixed-responders" the response was considered to end and relapse to begin, on a particular date obtained from a consideration of all other available data,

especially x-rays. The "remission" phase was considered to begin arbitrarily, on the eighth day after implantation. In the "non-responders", the "post-ablation" phase was arbitrarily considered to begin on the eighth day also.

For each patient, the site of metastases was determined on two occasions. At the time of implantation, the presence of bone deposits, as seen radiologically (Chapter XII), was ascertained. At autopsy, this was checked, as well as note made of the presence of liver deposits.

ENZYME ASSAY METHODS AND UPPER LIMITS OF NORMAL

ENZYME	UPPER LIMITS OF NORMAL (and basis)	METHOD USED
TAP	3.1 K.A. units/100ml. (mean +2 S.D. 65 normals)	King and Jegatheesan (1959)
PGI	30 Bodansky* units (mean +2 S.D. 64 normals)	Bodansky (1954a)
PGM	82 Bodansky units (mean +2 S.D. 12 normals)	Bodansky (1957a)
Aldolase	8 units (authors of method)	Sibley and Lehainger (1949 a & b)
5-N	15 i.u./l. serum (mean +2S.D. 20 normals)	Campbell (1962)

* 1 Bodansky unit = 4.63 international units/litre.

RESULTS

The data have been analysed in four different ways:-

(1) To show any correlation between cancer remission or advance, and change in the serum enzyme level; and to compare the different enzymes in their reliability in this respect.

(2) To correlate the level of each enzyme with site of metastases, to ascertain any organ specificity.

(3) To compare the overall sensitivity of the various enzymes, in indicating the presence of metastatic cancer.

(4) To compare the extent of pre-implant abnormality (TAP only) with extent of (bone) metastases.

(1) Correlation of change in serial enzyme levels with change in cancer activity (Figs. XIV.1 and XIV.2).

In Figs. XIV.1 and XIV.2 the uninterrupted lines connect plots where the period of study exceeded eight weeks. Interrupted lines connect plots where the period of study was only five to eight weeks. The plots shown by closed circles represent the mean of the estimations on three to 23 different sera, usually six sera.

a. Total acid phosphatase (Fig. XIV.1).

All the data are shown in Fig. XIV.1. There is a total of 29 patients, of whom 22 were adequately studied with respect to a follow-up of over eight weeks. Plots are the means of two to 23 estimations. (There was one exception, case P.Fl. where there was but one pre-implant measurement, but a number of measurements immediately after implantation were similar). It will be seen that plots based on shorter periods of study, and fewer observations do in general agree with the more adequately studied cases.

If a significant fall be arbitrarily fixed at 1 K.A. unit, none of ten responders and "mixed" responders showed a change. On the other hand, three out of six responders, and one of three non-responders, showed rises in progressing to their terminal phases.

For the first year of this study, both formol-stable acid phosphatase (FSAP) and tartrate-labile acid phosphatase (TLAP) fractions

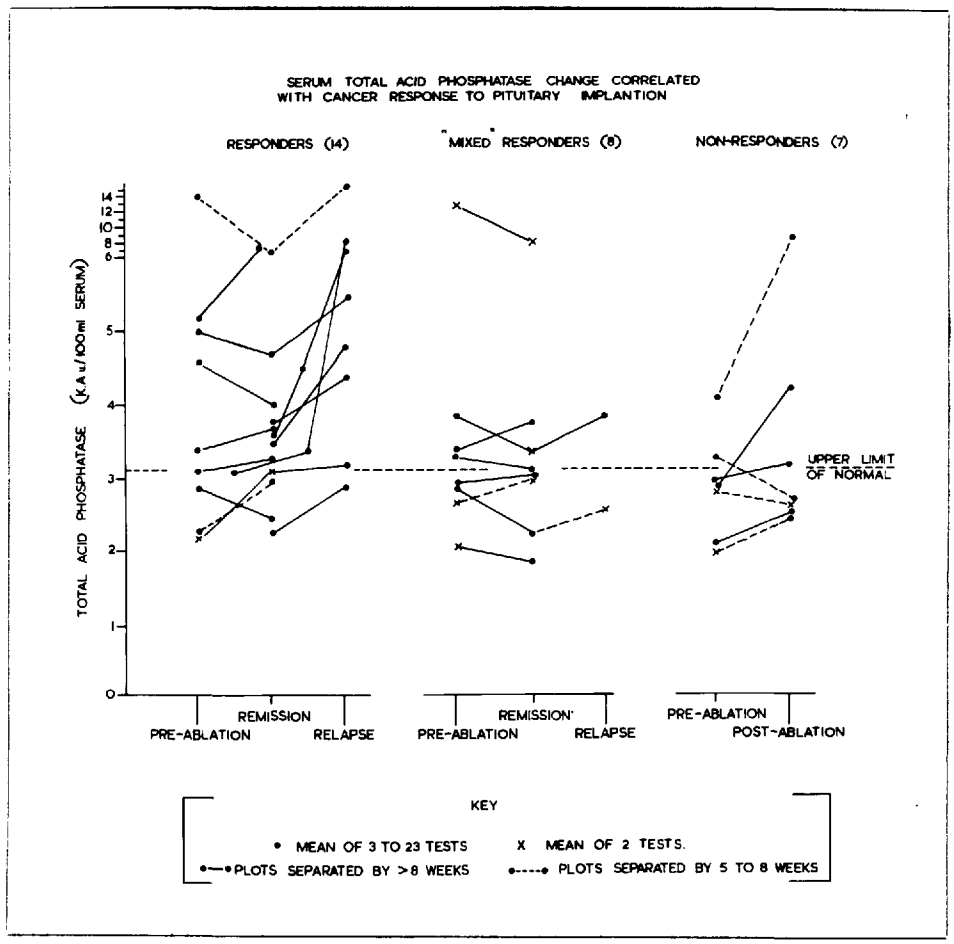


Fig. XIV.1. - If a significant change in an adequately studied patient is taken as 1 K.A. unit, no significant falls occurred in 10 cancer responses, and only four rises in 9 relapses.

were estimated by Dr. Jegatheesan (King and Jegatheesan, 1959) on all sera tested for TAP. 19 cases were studied serially, and diagrams prepared on the same lines as Fig. XIV.1. With one exception (case A.Cl.) FSAP exactly parallelled TAP . All TLAP plots were in the normal range, and showed no change with cancer growth.

b. Phosphaglucose isomerase (Fig.XIV.2)

All the results are shown inFig. XIV.2. A total of 30 patients were studied, 23 with an adequate period of study of over eight weeks. It is seen that plots based on smaller numbers or shorter follow-up periods agree with the others quite well.

Among the eight responders with pre-implant measurements followed for over eight weeks, there were six with clearly raised pre-implant levels. In five of the six with raised pre-implant values, there was a fall, ranging from 12 to 63 Bodansky units. However, in one case (I.Hu.) there was a clear rise. She was also exceptional in showing an unusually short,although radiologically striking, response to incomplete pituitary ablation, at three months after implant, at the time that the first post-implant skeletal x-rays showed clear sclerosis; the patient went into rapid general and radiological relapse immediately after this, and it is thus possible that she was in fact relapsing at the three-month stage. However, the subsequent fall in PGI when she was clearly relapsing cannot be explained. Seven of the responders were followed from the remission phase for over eight weeks into terminal relapse, and all reached abnormal levels, six showing marked rises. The rise in PGI levels at this phase appear a little greater than the initial falls during the "remission" phase, the range of rise being 10 to 160 Bodansky units (excluding the exceptional case I.Hu.)

Among the "non-responders", three were followed after implantation for more than eight weeks, and all showed a rise in PGI. One of the "mixed" responders had adequate terminal relapse data, and showed a clear rise also.

There is thus a total of six patients with raised pre-implant PGI levels, followed for eight weeks or more, during a grade A or B response, of whom five showed clear drop in enzyme level. There is a

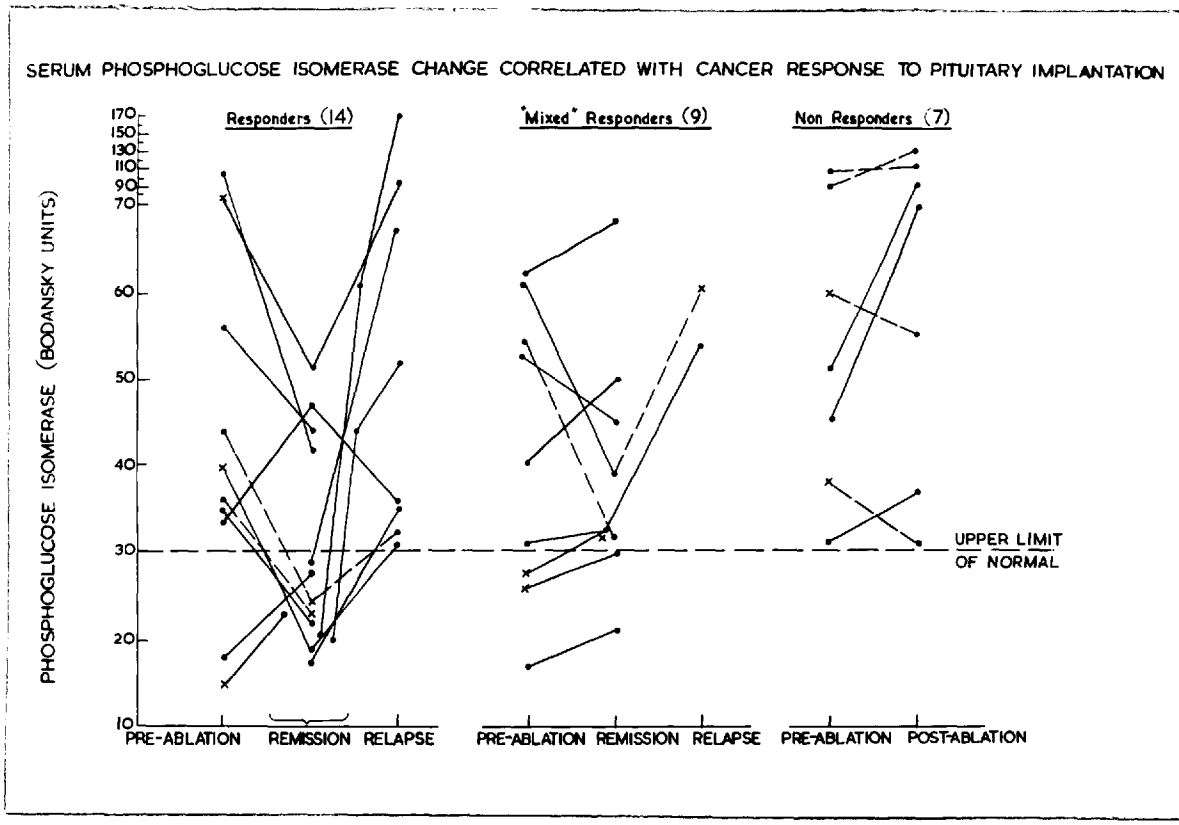


Fig. XIV.2. - See Fig. XIV.1. for the key to symbols. Considering patients followed for over eight weeks, five of 6 responders with raised pre-implant levels showed clear falls with cancer regression, while 10 of 11 patients entering their terminal illness showed rises to abnormal levels.

total of 11 patients from all the groups similarly followed into terminal relapse, of whom 10 showed rises. The discrepancies are both due to the one exceptional case, I.Hu.

c. Phosphoglucomutase.

Two to five pre-implant measurements were made on each of seven patients. In only two patients were the levels abnormal; the elevations were minimal. Only one responder was followed serially through remission to relapse, and all values remained within the normal range. Her serial data is shown in the Appendix, page 522. One non-responder was followed into terminal relapse, and showed a fall from 96 to 62 Bodansky units.

d. Aldolase.

Serial study was made on three responders, and three non-responders. Although in all but one case, the change in enzyme level agreed with the cancer response, all levels but one were within the normal range, making valid assessment of this enzyme impossible.

e. 5-nucleotidase.

Adequate serial study was only made on three responders. Only one had a raised pre-implant level, (E.Ti.), and this showed a clear fall from 18 to 10 i.u. One patient was followed into terminal relapse (I.Hu.), and showed a clear rise from 23 to 43 i.u. There is inadequate serial data to assess the value of this enzyme as an index of cancer response.

2. Correlation of enzyme level with site of metastases.

a. Total acid phosphatase.

In Fig. XIX.3 are shown all the pre-implant * values.

It is seen at once that abnormal levels (> 3.1 K.A. u.) are confined to patients with bone involvement; out of the 26 with bone disease, 17 had raised values.

On the other hand, when the group of seven patients with liver

* For cases C.Wi. (7 K.A.u) and M.Ro (4.8 KA.u) terminal TAP values were used.

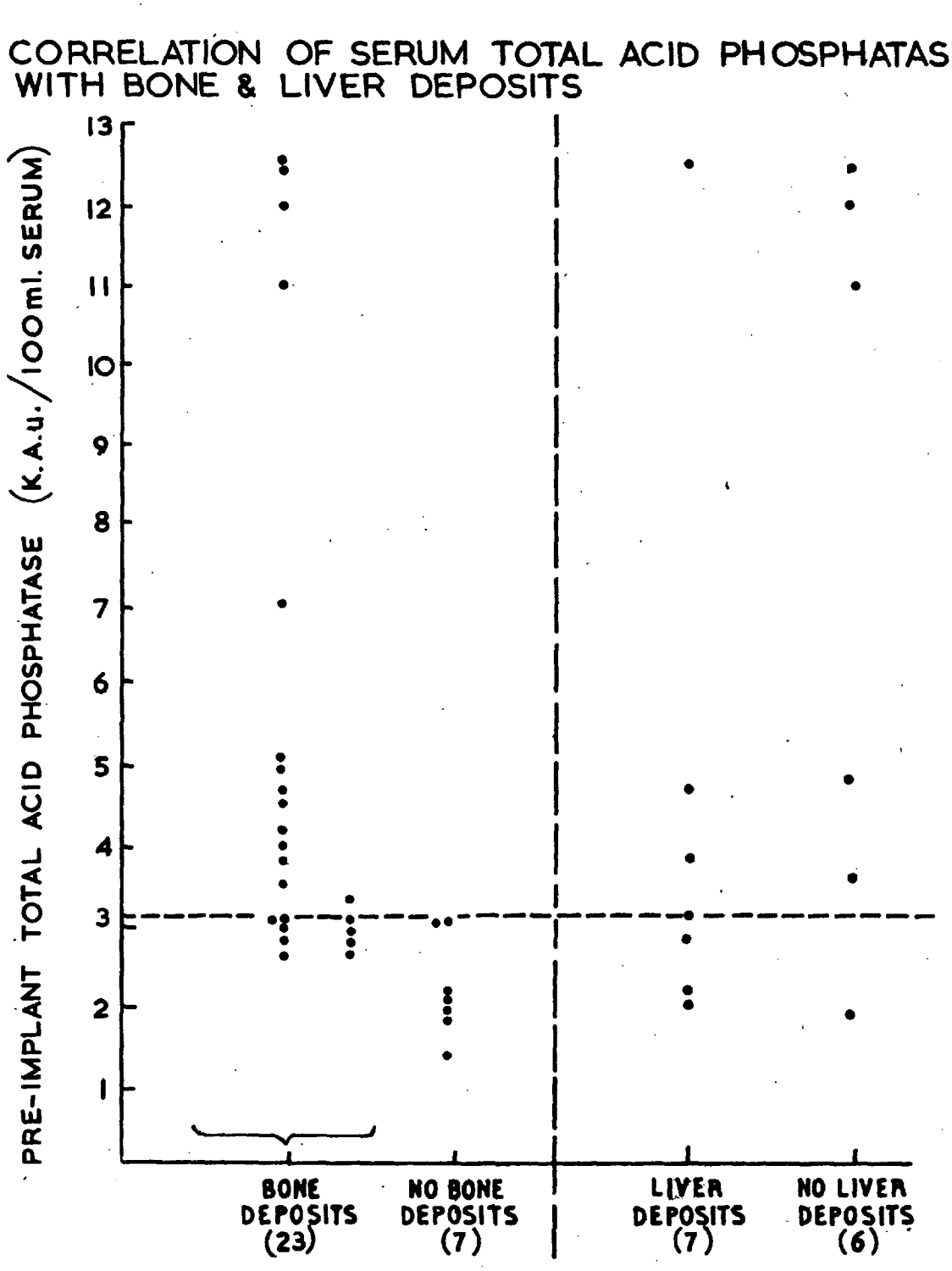


Fig. XIV.3 - Each plot is the mean of 2 to 7 pre-implant estimations on an individual patient. Presence of bone deposits was ascertained at the same time by x-rays, while presence of liver deposits was inferred from autopsy findings.

secondaries are compared with the group of six without, no difference between the two groups is seen. Both normal and raised values are seen within the group with liver deposits.

It can thus be concluded that raised TAP levels almost certainly mean that there are bone secondaries (16 out of 16), but that normal levels do not exclude bone deposits (9 out of 16 cases with normal values did have radiological bone lesions).

b. Phosphoglucose isomerase.

In Fig. XIV.4. each of the patients' mean terminal isomerase values are plotted, and grouped in columns according to the autopsy finding of bone and liver deposits. Values are the mean of all observations (2 - 7) in the last three months of life. Two cases, R.Eg., and L.To. are included, because, although autopsy was not done, enormous nobly livers were found just before death, and two became jaundiced. Two cases were omitted, as autopsy showed other liver diseases as well.

It is first evident that all the values are raised. When the nine patients with bone deposits are compared with the four patients without, no distinction is seen. On the other hand, when the eight with liver deposits are compared with the group of five without, it is seen that seven out of 8 with liver deposits exceeded 50 Bodansky units, while none out of five without liver deposits did so. Case C. Ke., the exceptional case with liver deposits, had a PHI of only 36 units; she died suddenly of another cause, and at a coroner's autopsy, only a few tiny deposits were found.

It can thus be concluded that values of over 50 Bodansky units indicate that liver secondaries are present.

c. Phosphoglucomutase, aldolase, and 5-nuclectidase.

Insufficient data was obtained to assess these enzymes in the above manner.

However, the proposal of Bodansky (1957a) that a high PGI:PGM ratio favoured bone deposits, and a low ratio favoured liver deposits

CORRELATION OF SERUM PHOSPHOGLUCOSE ISOMERASE WITH BONE & LIVER DEPOSITS.

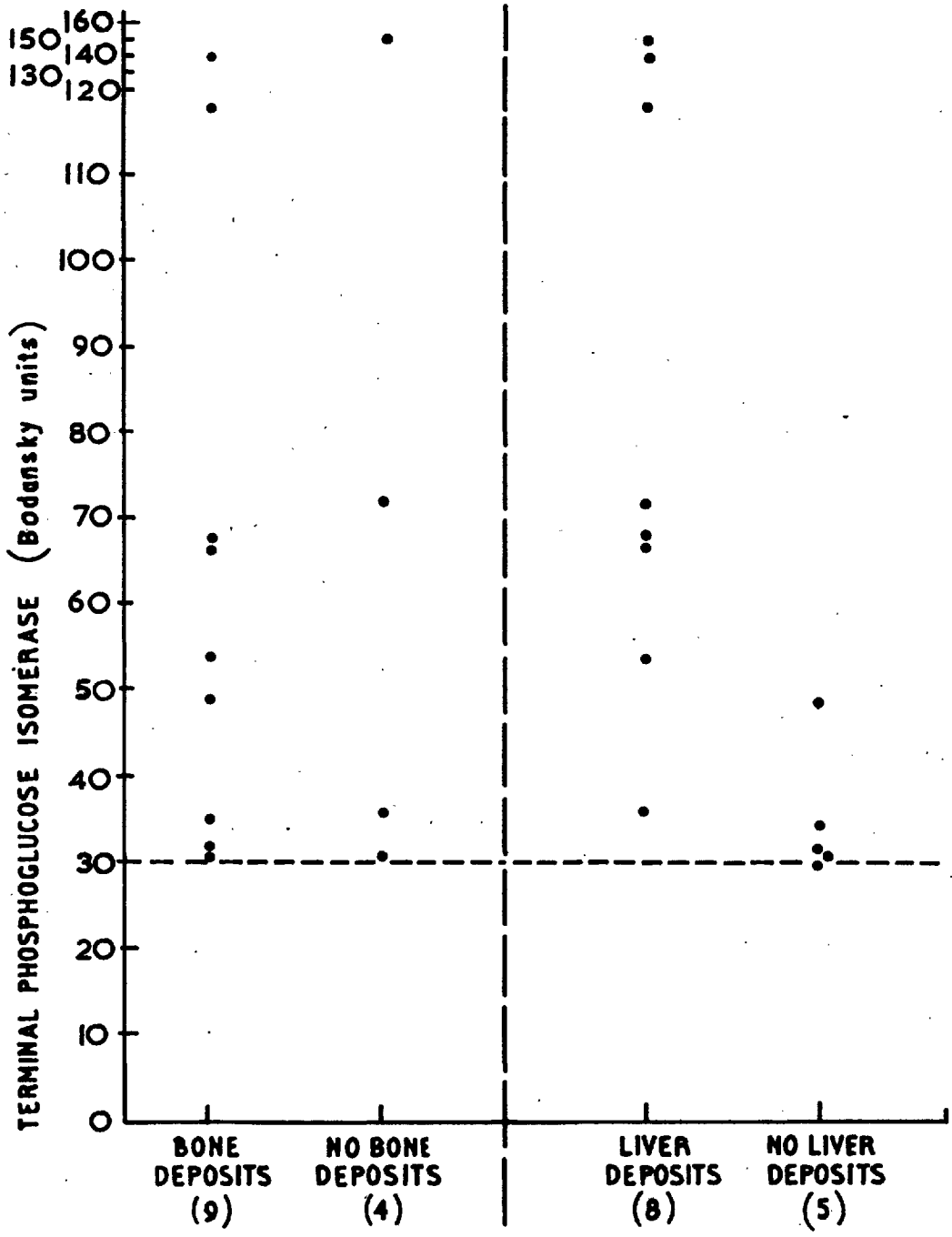


Fig.XIV.4 - Each plot represents the mean of all (2 to 7) estimations done within 3 months of death. The presence of bone or liver deposits was ascertained at autopsy in all cases.

could be tested in 14 patients. In Fig. XIV.5. these data are shown plotted. Only patients with two or more estimations of both enzymes are included. The actual numbers of estimations in each patient of PGI were 4 to 30 (mean = 8), and PGM 2 to 13 (mean = 4). Although autopsy information on the presence of liver deposits was only obtained for four patients (plotted as closed circles), two had liver involvement and two did not. The remainder only had clinical and biochemical evidence about liver deposits. It can be seen from Fig. XIV.5. that no distinction between bone and liver involvement is provided by the PGI:PGM ratio.

3. Comparison of sensitivity of the various enzymes in reflecting the presence of metastatic breast cancer. (Fig.XIV.6).

Pre-implant mean values for all patients in whom two or more estimations of any enzyme were made, are shown in Fig. XIV.6. Although the number of patients studied is small with respect to some enzymes, it is clear that PGI is the most sensitive to the presence of metastatic breast cancer, followed by TAP. Aldolase and PGM are too insensitive to be of practical value, while 5-N might be proven reliable by further study.

4. Correlation of pre-implant total acid phosphatase level with the radiological extent of bone deposits (Fig. XIV.7).

In 20 patients, more than three (mean = 4.5) estimations of TAP were made before implantation and skeletal radiographs taken. The radiographs were inspected, and the number of bone metastases assessed by the writer as "few", "massive", and "moderate" (i.e. neither "few" nor "massive").

In Fig. XIV.7 is shown the mean TAP for the twenty patients, plotted according to the rating of the skeletal involvement. It appears that markely elevated TAP is confined to those patients with massive skeletal disease, but clearly the converse is not true; extensive skeletal disease can occur with normal values.

CORRELATION OF PGI/PGM RATIO WITH BONE AND LIVER DEPOSITS

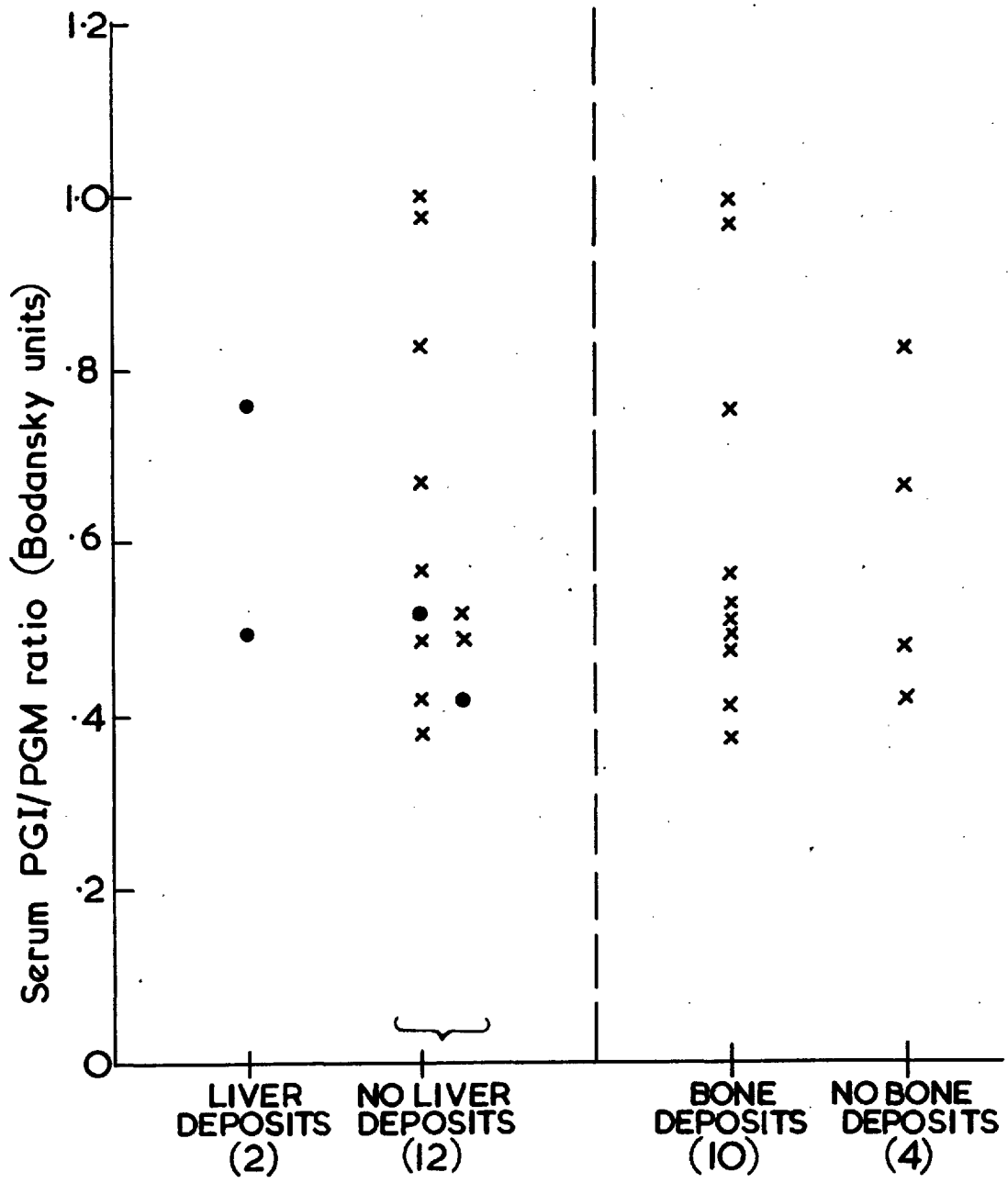


Fig.XIV.5 - Each plot is the ratio of PGI/PGM for one patient based on 2 to 30 simultaneous estimations of each enzyme. No correlation with site of metastases is shown. 4 patients in whom the site of deposits was found by autopsy are shown as closed circles.

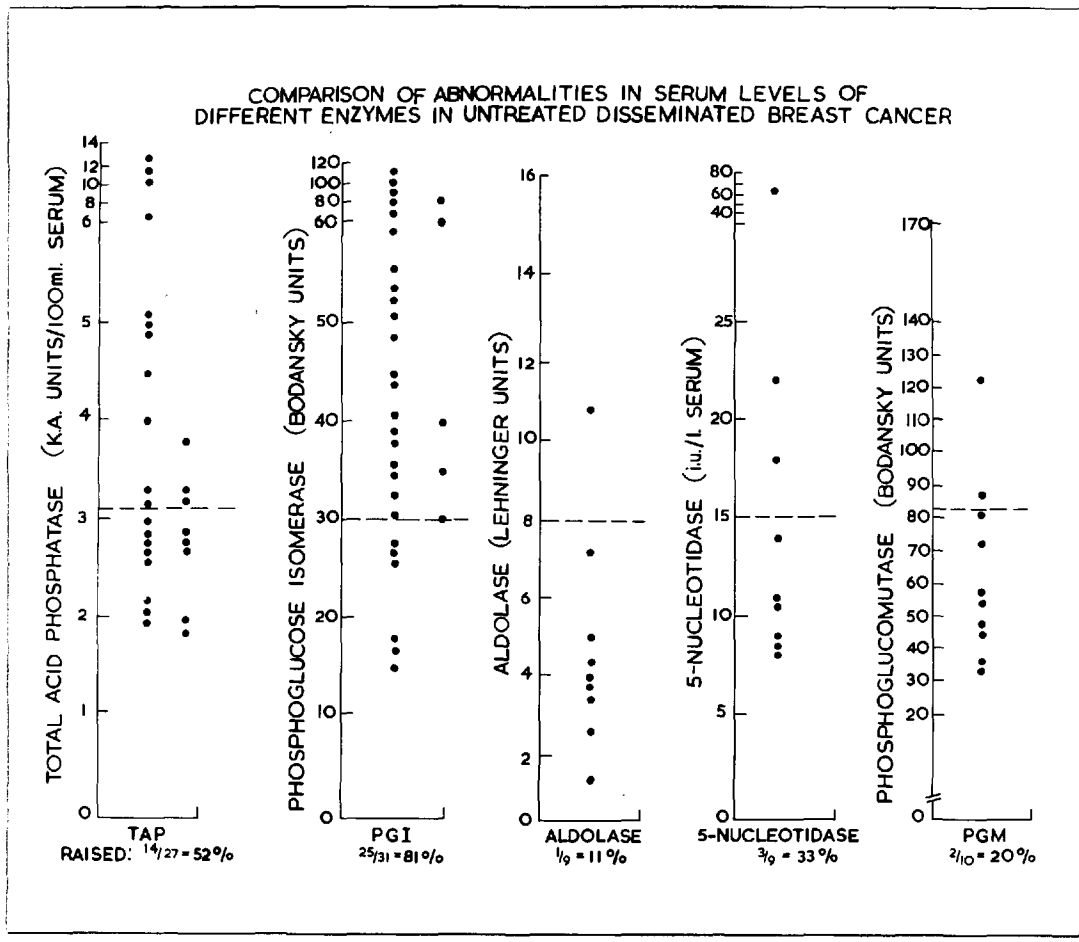


Fig. XIV.6 - Every patient who had two or more pre-implant estimations of any enzyme is included, and represented by a mean value.

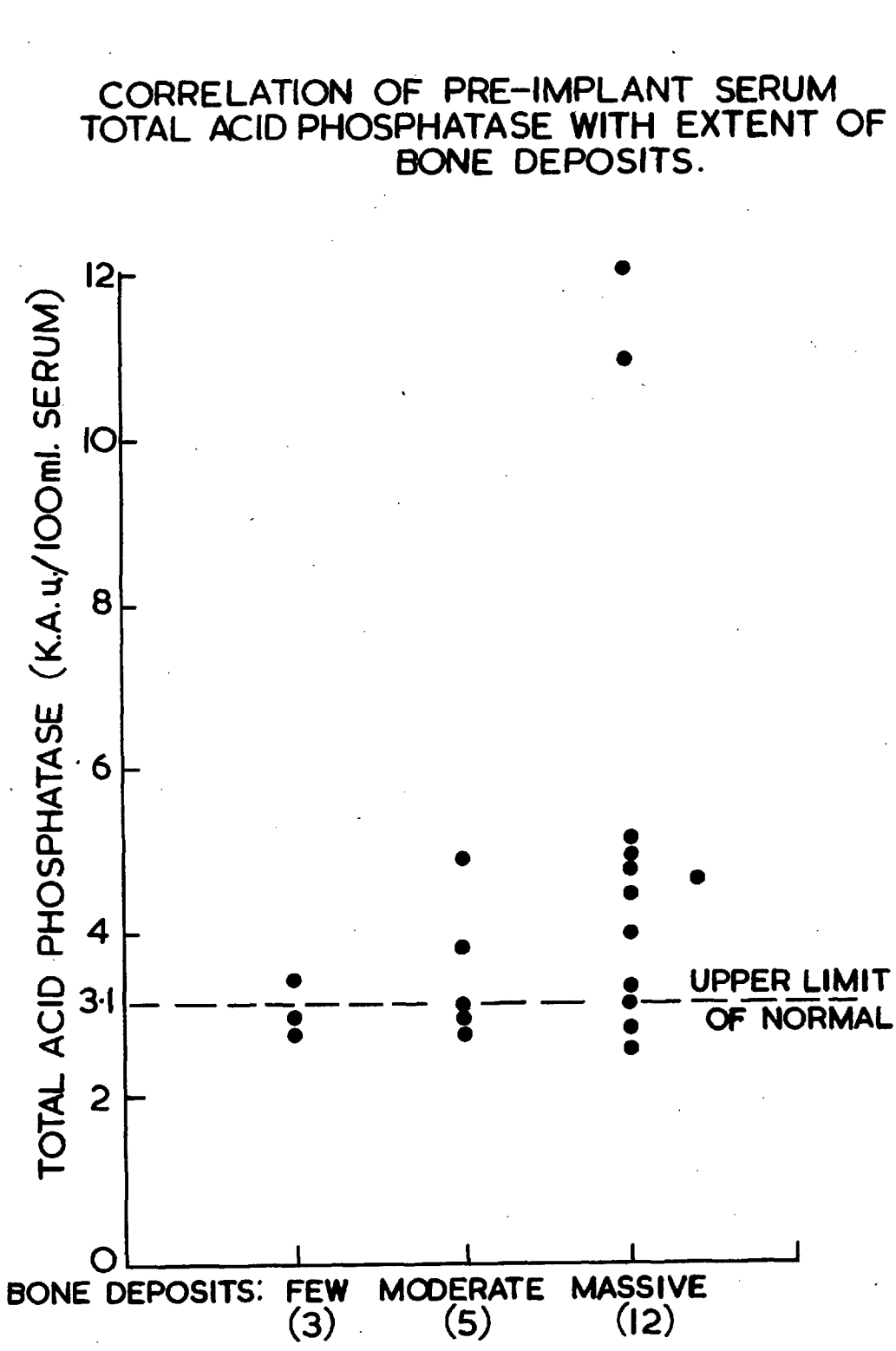


Fig.XIV.7 - Each plot is the mean of 3 to 7 estimations before implantation. The extent of bone deposits was visually quantitated from radiographs taken at that time.

DISCUSSION

There has not, hitherto, been a detailed exploration of serum enzymes as a means of following breast cancer progress. An early analysis has already been published (Joplin and Jegatheesan, 1962; Jegatheesan and Joplin, 1962). The present study has a great more data and reclassification of many patients as more data on the general response and from autopsy became available.

PGI

This merits serious consideration as an index of cancer activity. It has been shown that if estimations are made before pituitary implantation and found to be raised, and estimations are made over a period of the next eight weeks, a comparison between the mean values of the two phases will agree (8 out of 9) with the overall clinical assessment based on all other parameters available. The existence of the clinical category of a "mixed response" was associated with a variable PGI response, which includes clear rises and clear falls. Hence, if the only parameter for assessing breast cancer response were PGI, the clinical category of a "mixed responders" would be about equally divided between responders and non-responders. Of course, it is possible that this division of a clinically heterogeneous group, into responders and non-responders by PGI changes might in fact be more valid than the other parameters considered together. If the whole series of 12 adequately studied cases, with elevated pre-implant PGI levels is considered, there is only one case where the post-implant change in PGI is at serious variance with conventional parameters.

Following an initial remission phase, the next phase, that of terminal relapse, involves a much more striking clinical change, so it is not surprising that gross change in PGI levels may occur. In eight cases adequately followed from remission to terminal relapse, and associated with a raised PGI in the relapse phase, the PGI reflected this change in seven. There were substantial rises in some instances. An indication of the sensitivity of the PGI level to untreated disseminated breast cancer was provided by the finding shown in Fig. XIV.6. that 81% of 31 patients, with two or more pre-implant

estimations, a raised mean level was shown.

TAP

Of the other serum enzymes studied, the total acid phosphatase (TAP) appears the most sensitive to the presence of disseminated cancer, with 50% of patients showing a raised level pre-implant. Unfortunately this lesser sensitivity to the presence of metastatic cancer is also apparent when the cases are serially studied following implantation. Changes during cancer remission were small and showed no consistent correlation with the olinical improvement. However, when terminal relapse occurred, four out of nine cases showed a rise of more than 1 K.A. unit. A rise of this extent was invariably associated with terminal relapse.

The low sensitivity to cancer, of the remaining enzymes studied - aldolase, 5-nucleotidase, and phosphoglucomutase - made it difficult to assess their ability to reflect change in breast cancer. However, sufficient data was accumulated to discard aldolase and PGM on grounds of insensitivity, but the position with 5-nuoleotidase is still to be defined.

Organ specificity

The feature of organ specificity which emerged strikingly with both enzymes fully assessed - TAP and PGI - is of some interest. The former was shown (Fig. XIV.3) to be elevated exclusively in the presence of radiologically-apparent bone metastases, but that only about half the cases with bone metastases showed abnormal levels. Thus, the TAP is a less sensitive indicator of bone metastases than radiology. This lack of sensitivity, even to deposits in the most favourable site, bone, is no doubt the cause of its insensitivity to the rather small extent of bone healing in many of the responding cases. The only degree of change to which the TAP consistently responds is terminal relapse.

PGI seems to particularly reflect liver deposits, although moderately elevated levels are found in the absence of liver damage (Fig.XIV.4). Levels of over 50 Bodansky units occurred only in cases with liver deposits. The ratio of PGI/PGM was examined as an index of bone or liver involvement, but was not found valid. This suggestion was made

by Bodansky (1957b), based on his finding in tissues of a low ratio in normal liver, and a high ratio in normal bone, and supported by serum levels in three clinical examples.

The cause of raised serum enzyme levels.

It would appear from the present demonstration of a high degree of specificity of TAP for bone, that it is this host tissue which is almost entirely responsible for elevations of this enzyme. Tissue analysis for TAP by Dr. K. A. Jegatheesan (Jegatheesan and Joplin, 1962) showed that the concentration in a breast cancer deposit in bone was much higher than in the primary, or in normal bone or normal liver. It would thus appear that the interaction of the neoplastic tissue with the bone is responsible for the high tissue level, and hence, probably, the high serum level. He further showed that the type of acid phosphatase in the nuclei of the metastasis corresponded better with the type found in serum, than did the type found in the other subcellular fractions of the metastasis.

Somewhat similar investigation of the high PGI levels in the presence of liver deposits provided the following: although very high serum levels are confined to patients with liver deposits, moderate elevations can be found wherever the metastases are situated, thus suggesting that either the cancer tissue, or all host tissues, can liberate some PGI, but that the liver can liberate especially large amounts when damaged by the presence of metastases. Bodansky (1957a) found the tissue level of PGI to be twice as high in normal liver as in normal bone, while Dr. Jegatheesan found that both normal liver, and a breast cancer deposit in liver, contained many times more PGI than in the breast primary, or normal bone.

It would thus appear that both TAP and PGI appear in the serum largely as a consequence of the interaction of the deposits and host tissue. Only bone metastases are able to elevate the TAP, while liver metastases most strikingly elevate the PGI, although lesser elevations may occur when there is breast cancer tissue in any site. This contrasts with the raised serum acid phosphatase in prostatic cancer, which appears to be actively secreted by the malignant tissue

wherever it is found (Seligman and Manheimer, 1949).

Practical value of serum enzyme estimations.

The final point for discussion, and the main object of this study, is the practical value of these enzymes in the clinical management of breast cancer. PGI undoubtedly merits a place in the routine assessment of cancer response to pituitary ablation, in that it is nearly always abnormally high before treatment, and changes are significant. Additional and possibly useful information, is obtained from the association of PGI levels of over 50 Bodansky units with liver deposits. TAP on the other hand, in being less sensitive to the presence of cancer even in bone, provides no information which cannot be obtained from skeletal x-rays, and is much less sensitive to change. It thus does not merit a place in case study, where serial radiology is available. PGM and aldolase do not appear worthy of further study, but the 5-nucleotidase probably does.

SUMMARY

1. 11 women with disseminated breast cancer, who had either a good general cancer response to pituitary implantation, or no response at all, had 2 to 10 estimations of serum PGI before operation, and 2 to 12 after an interval of eight weeks. Out of nine patients with a raised pre-implant level, the change in level after implantation agreed with the cancer response in eight cases. Out of 11 patients similarly followed into terminal relapse, the change in PGI level agreed in 10.
2. Serum PGI was estimated on 2 to 7 occasions in the last three months of life, in 13 patients in whom autopsy examination of the liver was made. All of seven cases with mean levels of over 50 Bodansky units had liver deposits, while only one of six patients with levels below this had liver deposits (and these were small).
3. Serum TAP was similarly studied. No consistent fall occurred in the four fully studied patients who had a raised pre-implant level, and a good clinical response. Only four out of nine patients followed into terminal relapse showed rises of more than 1 K.A. unit.
4. Serum TAP was estimated on 2 to 7 occasions before pituitary implantation in 33 patients with an adequate radiological survey of the skeleton. Raised mean values (above 3.1 K.A. units/100ml. serum) were found in 17 out of 26 with skeletal deposits, but none of seven patients without. The highest values were found in those with the most numerous skeletal deposits.
5. Raised mean levels of the following serum enzymes were found before implantation: PGI 25 out of 31 (81%); TAP 14 out of 27 (52%); 5-nucleotidase 3 out of 9: PGM 2 out of 10: and aldolase 1 out of 9.
6. Frequent serial PGI estimations are recommended as being a valid parameter of breast cancer response after pituitary implantation.

CHAPTER XV

THE COMPLICATIONS FROM YTTRIUM-90 IMPLANTATION FOR TOTAL DESTRUCTION OF THE NORMAL PITUITARY GLAND

Four types of complication are possible from pituitary implantation - inadvertent irradiation damage to nearby vital structures, infections, and the consequences of misjudged endocrine replacement therapy and diabetes insipidus. In this chapter, the incidence of such complications will be reported, and analysed to show contributory factors. In addition, the "natural history" of the complications will be detailed. Diabetes insipidus is considered in Chapter XI.

The patients to be considered comprise all who had an yttrium-90 implantation with the object of total pituitary destruction, in the treatment of breast or other cancer and diabetic retinopathy. Where data is available, the very early implants are to be included as well. The series terminates in October 1962. The complications will be reported separately for each successive type of procedure that was evolved, and are the same groups as used for the report on extent of functional ablation in Chapter X, Table X.II. The transcranial surgical implants will not be considered, as although complications were numerous, their analysis throws no light on the complications of needle-implantation.

To a considerable extent, the various hazards of implantation have diminished with successive improvements in technique and further knowledge of the irradiation characteristics of the yttrium-90.

RESULTS

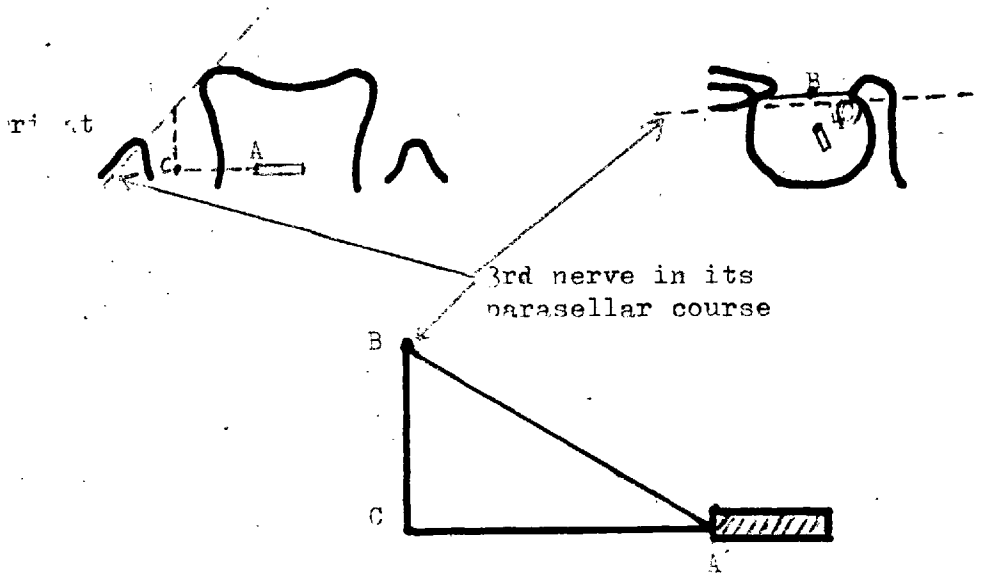
The main results are summarised in Table XV.I. The individual complioations will now be considered in more detail.

Oculomotor nerve paresis (Table XV.I and XV.II.)

The occurrence of oculomotor nerve paresis has now been eliminated. There was but a single example in the 55 implants done for disseminated breast cancer or diabetic retinopathy sinoe October 1959. In faot, there was only a total of nine instances of significant paresis altogether, and all can be attributed to poor accuracy of yttrium placement with the original method of multiple seed implants using the side-ejection needle; this was due to ignorance of the radiological position of the nerve, difficulty in locating the mid-line on screening with the original immobile image intensifier, and the variability in the direction in which the seeds emerged from the needle.

The occurrence of this complication can be explained by measurements on post-implant radiographs. Using the radiological criteria for the position of the nerve reported in Chapter II, the distance from the nearest seed to the nerve was ascertained as follows. In the straight antero-posterior film, the most lateral and highest seed was identified on the affected side. Usually this could be done quite easily, but occasionally it was necessary to refer back to the films taken during the implant. The distance of the seed below the third nerve was found from the lateral film, and its distance medially from the nerve was obtained from the 25° tilt film. These two measurements were corrected for magnification. They form two sides of a right-angled triangle, and so the hypoteneuse can be obtained (Pythagoras).

This is illustrated: Suppose point A on an yttrium seed is the nearest source to the right third nerve, B. The source is then the distance CB below the nerve on the lateral film, and the distance AC medial to the nerve on the antero-posterior film. The actual distance is BA, which is $\sqrt{CB^2 + CA^2}$.



The above measurements were made on x-rays for coulomotor nerves in patients with multiple seed implants (Table XV.II,) and show that the seeds were nearer to the coulomotor nerve in the cases of paresis, usually being within 3 mm. This implies that the nerve can tolerate an irradiation dose of about 100,000 rads, which is in agreement with the autopsy measurements of Chapter IV.

TABLE XV.I.

COMPLICATIONS FROM VARIOUS TYPES OF (FIRST) YTTRIUM-90 NEEDLE IMPLANTS (116 PATIENTS)

		C.S.F. leak or "meningitis"	Oculomotor paresis	Visual loss	Death due to implant: Surgical	Death due to implant: Metabolic	No. pts.	
Multiple Y-90 seeds 73% ablated	Very early (11) 29/5/56 to 23/4/57	4	2	3	0	0	11	CANCER
		0	0	0	0	0	0	D.M.
	Anatomy known (40) 16/7/57 to 22/9/59	11	7	3	1	0	40	CANCER
		0	0	0	0	0	0	D.M.
	Mobile image intensifier (10) 2/10/59 to 5/2/60	0	0	0	0	0	7	CANCER
		3	0	0	0	1	3	D.M.
Two long Y-90 rods 16% ablated	Diaphragm dose 100,000 - 150,000 rads (15) 26/2/60 to 9/12/60	0	0	0	1	0	9	CANCER
		0	1 *	0	0	0	6	D.M.
	Diaphragm dose 200,000 rads (9) 17/2/61 to 12/5/61	3	0	0	0	0	9	CANCER
		0	0	0	0	0	0	D.M.
70% ablated	Diaphragm dose 300,000 rads(21) 21/7/61 to 17/8/62	2	0	1	0	0	10	CANCER
		1	0	0	0	1	11	D.M.

* only lasted a few days

TABLE XV.II.

RELATION BETWEEN POSITION OF Y-90 SEEDS AND OCCURRENCE OF OCULOMOTOR PARESIS IN MULTIPLE SEED IMPLANTS.

		DISTANCE * FROM NEAREST SOURCE TO THIRD NERVE			
	No.of eyes	0-2.0	2.1-3.0	3.1-4.0	> 4.0
THIRD NERVE PARESIS	7	3	2	2	0
THIRD NERVE NORMAL	43	0	2	6	35

* corrected for magnification

The day of onset of the clinical paresis was noted in seven patients, and was between the 1st and 25th day (mean = 10 days). In most cases it improved over the ensuing months, and finally diplopia disappeared.

An interesting patient was case C.Wi. in whom a left third nerve paresis occurred on the 4th day. When re-examined 3½ years later (Fig.XV.I) the nerve had partly regenerated, but some axons must have entered the wrong branches, because when asked to look downwards, the lid of the affected eye failed to drop as far as it should, and contraction of the left pupil was induced by asking her to look to the right and upwards.

Optio nerve damage (Table XV.I and Fig. XV.2).

Visual acuity was routinely tested in all patients before and after implantation, and in addition most of the early cases also had perimetry done. This is less sensitive than a Bjerrum screen examination but it could be performed with more rapidity and would certainly show important defects.

In Table XV.I. it is shown that there were a total of seven patients, out of the 116 implanted, who sustained visual defects. With an isolated exception (which was probably not due to the implant and was, indeed, unsuspected by the patient), this complication was confined to the early multiple seed implants. In every case post-implant films showed that seeds had actually been implanted at, or even above, the

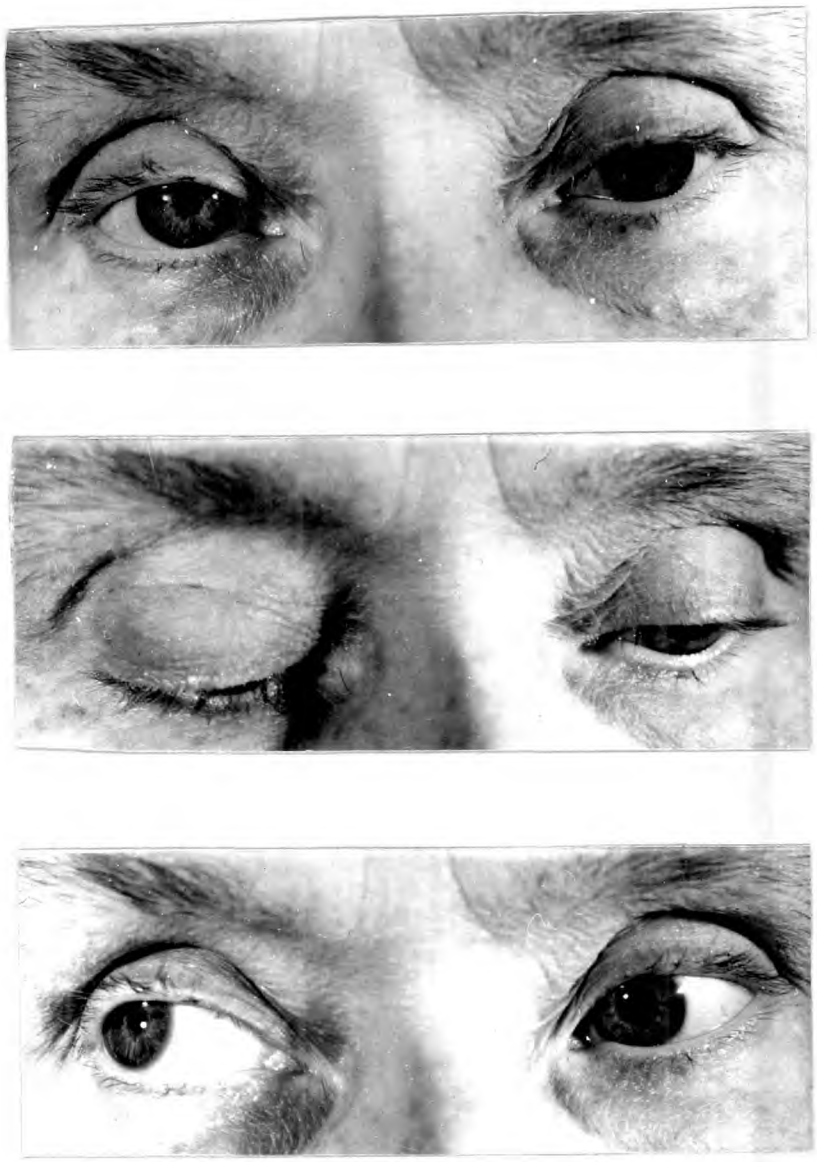


Fig. XV.1 - Case C. Wi., examined 3½ years after a multiple seed pituitary implantation for very advanced breast cancer. A left third nerve paresis had occurred on the 4th day. Above: "look ahead" - there is slight remaining ptosis and pupil dilatation. Middle - "look down" - the left lid fails to drop normally. Below: "look up and to the right" - the left pupil contracts.

level of the diaphragma sellae; three also had rhinorrhoea or meningitis. There was no case of visual loss where the highest seed was clearly below the normal radiological position of the diaphragma sellae. If the tolerance of the chiasma is similar to the oculomotor nerve, i.e. about 100,000 rads (Chapter IV), and as the average irradiation intensity used was 100,000 rads at 3mm, it could be deduced that the inferior border of the chiasma is usually at least 3 mm. above the pituitary surface. An example of misplaced seeds causing optic nerve damage is shown in Fig. XV.2. The patient (case G.Gi) developed a bitemporal hemianopia on the 7th day and slight C.S.F. rhinorrhoea on the 33rd day. She died of very advanced cancer on the 38th day. There are two seeds embedded in fibrous tissue actually on top of the diaphragma sellae.

Cerebrospinal fluid rhinorrhoea.

This was by far the most serious and perplexing problem encountered with this operation as it carries a risk of meningitis. Only two instances of meningitis without known C.S.F. rhinorrhoea occurred, so the two conditions can be regarded as a single problem.

In Table XV.I it is shown that this complication occurred in a total of 24 patients in the 116 implanted. Its incidence fell as more experience led to modifications of the technique. In the final series of 21 patients there were only three cases, and this is to be viewed in the light of 70% having had "complete" functional ablation.

The delay (see later) between operation and onset of this complication indicates irradiation rather than direct trauma as the cause. The two points at which the irradiation dose is critical in the genesis of this complication are the needle-holes, and diaphragma sellae (Chapter IV). An analysis was therefore made of the irradiation dose delivered to these points, by measurements on post-implant radiographs. The radiographs of patients treated with multiple seeds could not be usefully analysed with respect to the needle-hole dose, as practically every patient had seeds virtually touching the anterior fossa wall, so these implants will be analysed separately first.

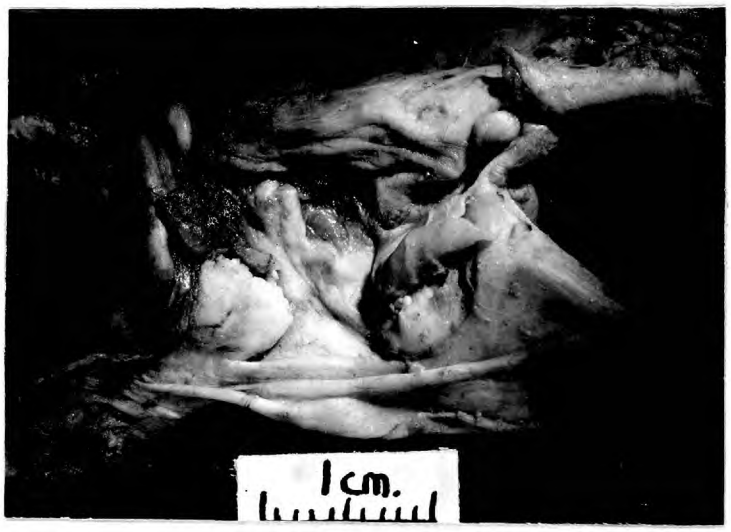


Fig. XV.2. The pituitary area, as seen from above, at autopsy (case G.Gi.) There is a large natural operculum in the diaphragma sellae. A pair of Y-90 seeds is visible embedded in fibrous tissue on the right side of the diaphragma sellae, and had caused bitemporal hemianopia.

Measurements of dose to the diaphragma sellae could be but approximate owing to the presence of multiple sources. Measurements were made of the distance from the nearest point on the uppermost seed to the "normal" radiological position of the diaphragma sellae.

(a) Multiple seed implants

The findings with the cancer patients treated with multiple seed implants are shown in Table XV.III. All 41 with satisfactory post-implant radiographs are included with the proviso that those who did not sustain these complications are shown only if they survived over 42 days (most patients developing rhinorrhoea do so within this time).

TABLE XV.III

RELATION BETWEEN THE POSITION OF Y-90 SEEDS AND OCCURRENCE OF C.S.F. RHINORRHOEA OR MENINGITIS IN 41 MULTIPLE SEED IMPLANTS FOR CANCER.

		DISTANCE (mm) OF HIGHEST SEED FROM DIAPHRAGMA SELLAE			
	No. cases	0-2.0	2.1-3.0	3.1-4.0	>4.0
RHINORRHOEA OR MENINGITIS	16	8	5	3	1
NO RHINORRHOEA OR MENINGITIS (AND SURVIVED >42 DAYS)	25	17	4	3	1

This complication is shown to occur with distances of the uppermost seed from the normal radiological position of the diaphragma sellae up to 5 mm., and there is no clear dividing line evident between those who sustained this complication and those who did not. This may be due to lack of proportionality between the actual dosage, and the measured distance between highest seed and diaphragma sellae. Such

variability may be due to the impossibility of measuring the contribution of irradiation from seeds adjacent to the highest, and in rare cases, gross error occurs in the estimation of the position of the diaphragma sellae, as illustrated in Chapter II, Fig. II.10. In addition to these variables in estimating the irradiation dose to the diaphragma sellae, there is the existence of an equally important second factor in the genesis of C.S.F. leakage, namely the patency of the needle-holes.

(b) Implants with two long rods.

With the patients who had implants with two long rods, fairly exact dosages at both the needle-holes and diaphragma sellae could be calculated. The results are shown in Fig. XV.3. where the dose at the most heavily irradiated needle-hole and peak dose to the diaphragma sellae are plotted. X-rays of additional patients with C.S.F. leakage in Dr. Robert Morrison's patients have been included so as to supplement the number of cases of the present series. Measurements were made for 19 patients who had a C.S.F. leak and 19 who did not. It is evident that the dose to both the diaphragma sellae and needle-holes was 300,000 rads or higher in 16 of the 19 with a C.S.F. leak, but in only 7 of 19 who did not. Thus out of 23 patients where the dose of 300,000 rads was exceeded both at a needle-hole and at the diaphragma sellae, a C.S.F. leak occurred in 16, whereas out of 25 patients where these doses were not reached, only three had such leaks.

"Natural history" of C.S.F. leakage

The time of onset of C.S.F. leakage and of meningitis could be established in 29 patients with one implantation for breast cancer. The results are shown in Table XV.IV, where it is seen that the two complications occur at about the same time interval after the operation (as a generalisation). Patients appear to be at risk from the day of implant to the 10th week. (The two patients in whom C.S.F. leaked up the implant needle during the operation were not included in this analysis).

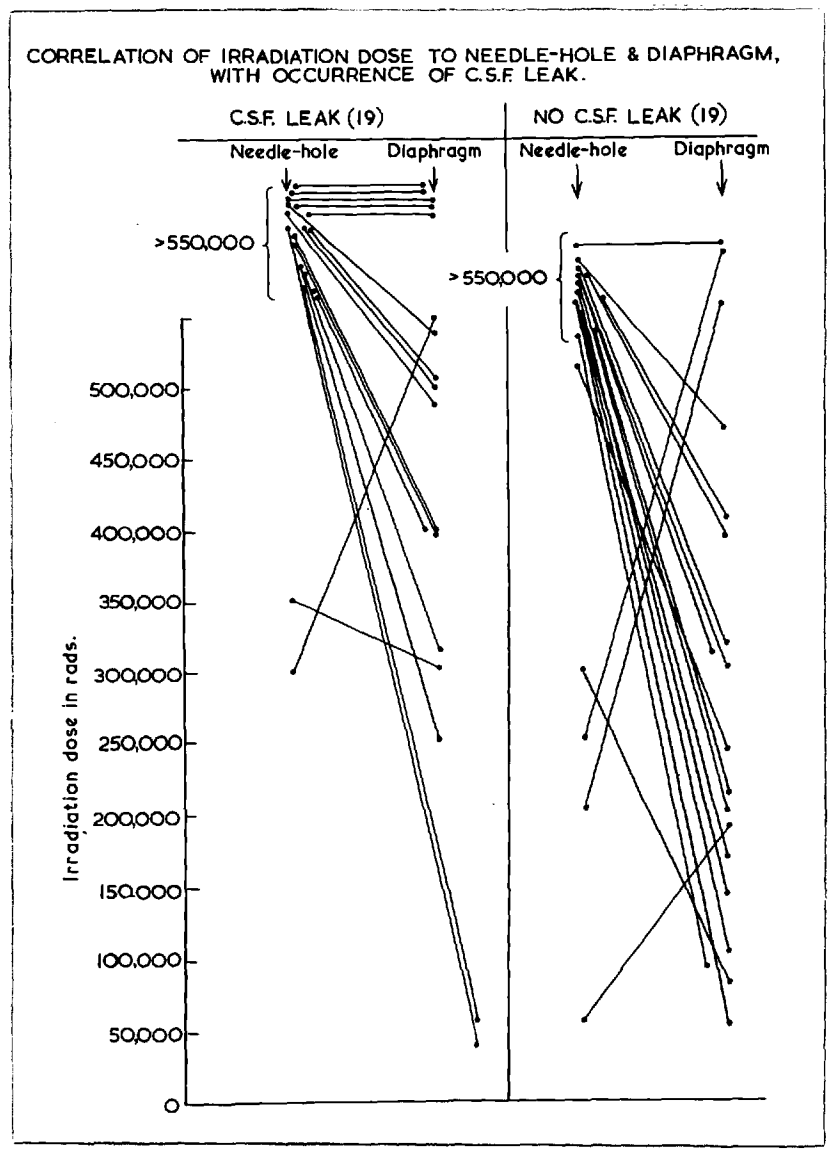


Fig. XV.3. From post-implant radiographs, the irradiation dose at the most heavily irradiated needle-hole, and the peak dose at the diaphragma sellae, was calculated and plotted.

TABLE XV.IV.

TIME OF OCCURRENCE OF C.S.F. RHINORRHOEA OR MENINGITIS AFTER (FIRST) YTTRIUM-90 IMPLANTATION IN BREAST CANCER

		No. cases noted	DAYS POST-IMPLANT			
			Earliest	Latest	Mean	90% between
C.S.F. leak	Onset	14	7	200	42	12 & 72
	Spontaneous cessation	6	56	210	138	
Meningitis	Onset	9	1	90	40	1 & 72

An example of this type of complication is case T.Su. The appearance of his sella at autopsy is illustrated in Fig. XV.4. He had had an implant of 14 3 mm. seeds of Y-90 by means of the side-ejection needle. Each seed gave a broadside-on dose of 100,000 rads at 3mm. On the 70th day, a slight C.S.F. rhinorrhoea appeared, and seemed to be coming from both nostrils. Post-implant radiographs showed that the highest seed was only 2 mm. below the normal radiological level of the diaphragma sellae and seeds were touching the needle-holes. From this it was inferred that irradiation from the high seeds had caused a perforation in the diaphragma sellae. In Fig. XV.4.(above left), the seed responsible for this damage is visible through the perforation in the diaphragma sellae. Two screws were inserted and the leak was arrested; they are seen in Fig. XV.4. (above right). The patient died of disseminated prostatic cancer in the 14th week. For comparison, a photograph of needle-holes in another patient is shown (below), to demonstrate the cleanly-drilled holes.

The "natural history" and response to treatment of C.S.F. leakage is detailed below for 18 patients with full records implanted for breast cancer, since July 1957. In 16 of them the leakage developed

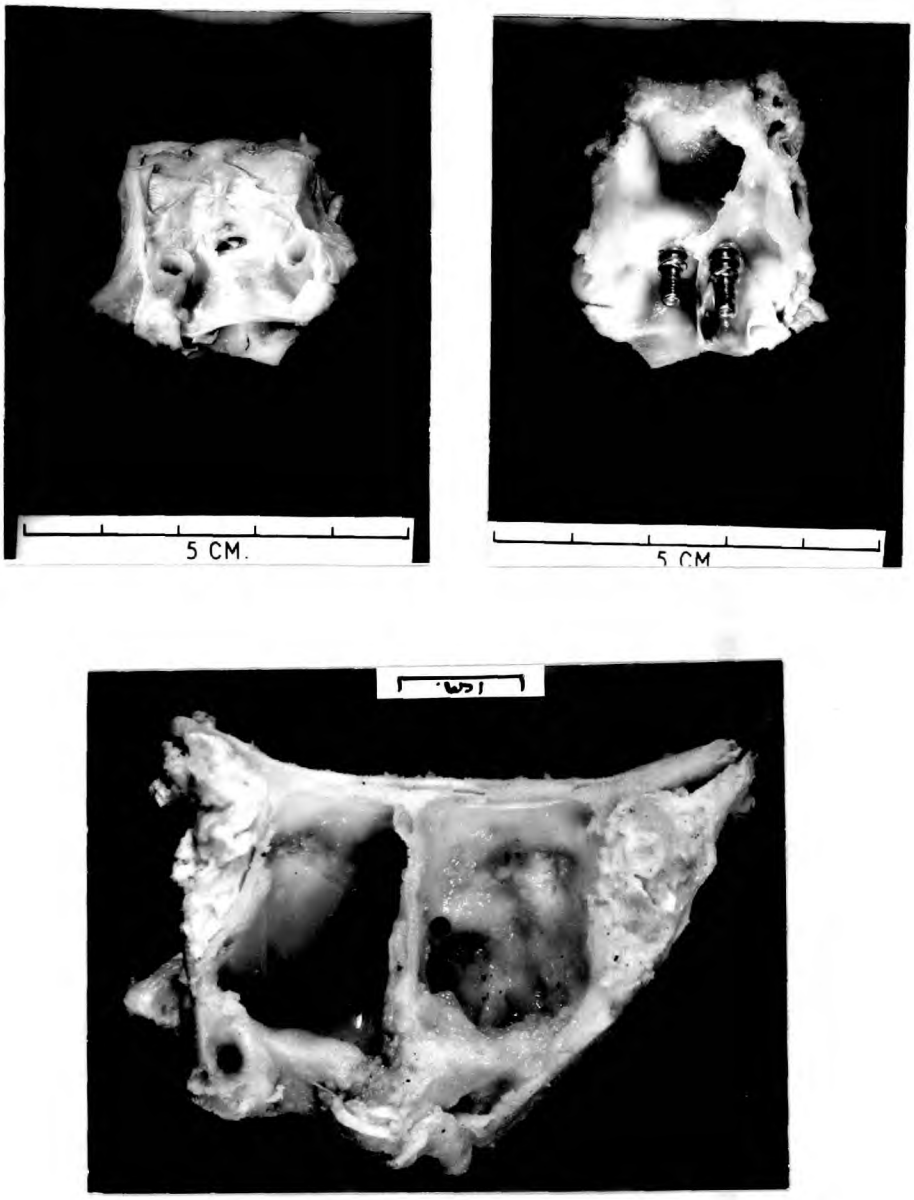


Fig. XV.4. The top pair of photographs show the autopsy appearances of the excised sphenoid in case T.Su. The one on the left is taken from above, and shows the perforation in the diaphragma sellae through which the seed responsible is visible. The picture on the right shows the two screws in position. Below is seen the cleanly-bored needle-holes in another patient; the photograph is taken from in front, and the mucosa has been dissected off.

after a first implant, and in two it was after the second. (There were two patients who developed meningitis without an obvious C.S.F. leak, and hence do not appear in this analysis).

No. cases with C.S.F. leak	18
Stopped spontaneously without meningitis	3
Led to meningitis	6
Leak ceased after meningitis	4
Screw insertion attempted	8
(a) Leak ceased	5
(b) Leak almost ceased	1
(c) Leak persisted	1
(d) Surgical closure required	1

It is of interest to note that in the group of five patients whose leak was successfully arrested by the insertion of a screw, three had a screw inserted only in the side from which the leak appeared to be coming. If the patient's statement about which nostril (or if both nostrils) discharges C.S.F. is used as a guide to which (or both) side of the fossa is to be plugged, 11 out of 11 nostrils were oorrectly assigned to the leaking side of the fossa.

Conservative treatment of C.S.F. rhinorrhoea was done in most patients by posture in the supine position for at least two days with the foot of the bed elevated one foot. It was only successful in two cases.

Meningitis

This was a clinical syndrome occurring after implantation, and nearly always in association with C.S.F. rhinorrhoea; it consisted of mild, moderate, or severe headache, neck stiffness and mild fever. Lumbar puncture yielded sterile C.S.F. and was usually under normal pressure.

To evaluate the C.S.F. findings in the presence of this clinical syndrome, a number of C.S.F. examinations were also made in unaffected (non-diabetic) subjects who had no such clinical signs. Ten examinations

were made in eight unaffected subjects between the 6th and 45th days. The results are shown in Table XV.V.

TABLE XV.V.

C.S.F. EXAMINATION AFTER IMPLANTATION FOR CANCER, IN ABSENCE OF CLINICAL MENINGITIS OR C.S.F. LEAK

Patient	Days post implant	Pressure (mm.water)	Naked eye	Total cells	% polys	protein (mg.%)	sugar (mg.%)	culture
M.Th.	19	120	clear	nil	nil	157	55	sterile
G.Gi.	7	-	clear	nil	nil	120	40	sterile
M.Ev.	11	90	clear	50	3	1210	53	sterile
L.LA	6	180	clear	nil	nil	47	63	sterile
M.Eh.	6	140	clear	nil	nil	-	-	sterile
E.No.(1)	16	"normal"	opal-escent	12,500	90	460	28	sterile
E.No(2)	45	"normal"	opal-escent	2,100	94	450	34	sterile
G.Wa(1)	13	-	-	nil	nil	64	-	-
G.Wa(2)	44	-	clear	nil	nil	93	-	-
E.He.	10	60	clear	nil	nil	85	45	sterile

It is evident that the C.S.F. may contain numerous cells and a large amount of protein reflecting the effect of irradiation, although it may be entirely normal. Examinations were made on the 4th and 5th days in

two diabetics because of a mild fever, and showed no cells and a protein of 50 mg% and 127mg% respectively.

Next, the C.S.F. findings in a series of patients who did have a clinical meningitis syndrome are shown in Table XV.VI. Although some patients were very ill with what clinically appeared to be acute meningitis, in two instances the C.S.F. was clear, and it was always sterile. Presumably the infection becomes rapidly localised to the pituitary area.

TABLE XV.VI.

C.S.F. EXAMINATION AFTER IMPLANTATION FOR CANCER, IN PATIENTS WITH CLINICAL MENINGITIS

Patient	Days post implant	Pressure (mm.water)	Naked eye	Total cells	% polys	Protein (mg.%)	Sugar (mg.%)	Culture
Non-Diabetics								
G.C-W(1)	39	-	turbid	5,850	"mainly"	550	111	sterile
(2)	64	-	turbid	850	-	80	53	sterile
A.Cr.	78	"high"	green-yellow	500	100	-	-	sterile
M.Mo	1	160	hazy	60	65	130	47	sterile
S.Jo.	90	-	purulent	3,000	90	-	-	sterile
C.Wh.	2	50	xantho	"++"	-	96	-	sterile
L.La.	72	-	clear	"++"	-	330	20	sterile
L.Eg.	6	175	clear	20	95	80	56	sterile
A.Cl.	16	-	hazy	820	100	130	45	sterile
Diabetics								
D.Hi.	59	60	hazy	44	nil	170	180	sterile
R.We.	3	-	-	nil	nil	100	-	sterile

No patient in this series died during the course of such an attack of meningitis, although autopsy examination of the pituitary area was only subsequently obtained in the case of A.Cl., where there was unmistakable evidence of previous infection. In this patient death was partly

attributable to the infection.

In three non-diabetics (M.Mo., C.Wh., and L.Eg.) the syndrome developed in spite of the routine post-operative streptomycin and sulphadiazine cover, while in the remainder no antibiotics were being taken at the time.

Treatment of the condition was uniformly effective, once an appropriate antibiotic was found. In seven episodes, chloramphenicol plus sulphadiazine or penicillin were used initially, and in six the condition rapidly settled, the exception requiring celbenin and vancomycin.

Without recurrence of C.S.F. rhinorrhoea, further episodes did not occur.

Diabetics seemed more prone (12 out of 20 specially observed) to early post-operative symptoms of headache, slight fever, and slight neck stiffness; there were only two with all these features, and their C.S.F. examinations made at the time are included in Table XV.VI. It was later found that these features were greatly reduced if higher post-operative dosage of steroids were given; it is probably caused by a greater steroid requirement in the diabetic state.

Complications of re-implantation (Table XV.VII).

A total of 15 patients with cancer and one with diabetic retinopathy had a second implant. All were planned to totally irradiate the gland with the ablation dose currently in vogue, irrespective of the position of the previous seeds. It can be seen from Table XV.VII that complications from re-implantation were not greater than with first implants (Table XV.I).

Complications from hypopituitarism

There were no deaths from omission of replacement therapy, although there were a few instances where intercurrent infection caused unnecessary disability from failure to elevate the steroid dosage *

* "steroid cards" were issued to patients, stating the preparation and dose being taken, and advice on care in the event of illness.

Very occasionally, a mild Cushingoid state resulted from a period of cortisone administration in doses above the 25 to 37.5mg./day required for normal replacement. This was necessitated by prolonged or recurrent infection. It was never necessary to give more than 0.3mg. thyroxine/day, and usually 0.2mg. sufficed.

Diabetes insipidus was unusual, never severe, and never permanent (see Chapter XI).

TABLE XV.VII.

COMPLICATIONS FROM RE-IMPLANTATION FOR BREAST CANCER

		No. re-implants done	C.S.F.leak or meningitis	Oculo-motor paresis	Visual loss	Death due to re-implant
Multiple Y-90 seeds	Very early 29/5/56-23/4/57	nil	-	-	-	-
	Anatomy known 16/7/57-22/9/59	4	0	1	0	0
	Mobile image intensifier 2/10/59-5/2/60	1	0	0	0	0
Two long rods	Diaphragm dose 100,000 rads to 150,000 rads 26/2/60-9/12/60	3	0	0	0	0
	Diaphragm dose 200,000 rads 17/2/61-12/5/61	3 *	0	0	0	0
	Diaphragm dose 300,000 rads 21/7/61-17/8/62	5	2	0	0	0

* includes one diabetic

There were two deaths in diabetics, arising as an indirect consequence of hypopituitarism. One (case D.Hi.) died from a mismanaged hypoglycaemic

episode, and the other (case C.Hi.) died from attempts to correct severe postural hypotension. These will be detailed in Chapter XVI.

No loss of energy or initiative was noted in those on replacement therapy. Those cancer patients who obtained really substantial cancer remissions were able to return to responsible and skilled employment. A few male diabetics who lost potency from the implant did not obtain full restoration with intramuscular or oral testosterone.

Anaesthetic complications

A total of 118 patients had an anaesthetic for total pituitary ablation for disseminated cancer or diabetic retinopathy. There were no anaesthetic deaths, nor deaths within 24 hours of the procedure. The procedure was abandoned in one patient, who had very advanced diabetic retinopathy and ischaemic heart disease, because of temporary ventricular asystole during the induction of the anaesthetic. She made a complete recovery.

Complications from surgical trauma

In a second diabetic (case Z.Mo.) as soon as the implant needle entered the pituitary gland, a brisk flow of C.S.F. emerged. A screw was at once inserted, and the leakage ceased. There was a temporary recurrence a few months later. There were two other patients in whom C.S.F. emerged from the implant needle during the operation. In case C.Wh. the C.S.F. appeared as soon as the second rod had been implanted. No screw was inserted. She died two days later, having failed to regain consciousness, and shown clinically a meningitis-like syndrome, with a clear C.S.F. No sign of meningitis was found at autopsy, and as the presence of C.S.F. leakage post-operatively could not be ascertained either clinically or at autopsy, the cause of death was not proven. In the other patient (case I.La.), a few drops of clear fluid emerged as soon as the implant needle entered the gland. A small leakage continued post-operatively, and so a screw was inserted, and this arrested the leakage successfully.

Haemorrhage from the nose was severe in a single case (D.Da.) and necessitated blood transfusion. It was likely that this was a consequence of her having previously fractured her nose several times.

DISCUSSION

From the experience reported here, it is evident that oculomotor and optic nerve damage are no longer encountered. The early examples are readily explained by considerably misplaced seeds; this degree of error can now be avoided.

The problem of meningitis was found to be really a complication of C.S.F. leakage. Even although the organism was never cultured from the C.S.F., it was successfully treated with antibiotics; with one exception, chloramphenicol with either sulphadiazine or penicillin was effective. The main points in the diagnosis were the clinical signs of fever and meningitis, usually with the C.S.F. findings, other than culture, corroborating. However, occasionally the C.S.F. was clear along with such a syndrome (Table XV.VI); presumably there was a localised pituitary abscess amenable to antibiotic therapy. There were occasional subjects without such a syndrome yet with a C.S.F. pleocytosis and high protein content, presumably due to irradiation of the meninges covering the pituitary gland. However, the C.S.F. is usually clear during normal convalescence.

In this series of 116 implants, there were but two deaths which could be attributed to the procedure. Both patients had advanced breast cancer. One (case C.Wh.) had a sunken pituitary and C.S.F. emerged at operation; no screw was inserted and she failed to regain consciousness. The other (case A.Cl.) had sustained severe meningitis which did, however, resolve before her death. There were no deaths during the operation, or in the first 48 hours. In view of the terminal condition of the majority of the cancer patients, this is a remarkable tribute to skillful anaesthesia.

The most important complication is C.S.F. leakage. The data suggest that this complication could be reduced to minor proportions by ensuring that the irradiation dose to the diaphragma sellae and also to the needle-holes is just under 300,000 rads. Attention to the former has reduced the incidence to the present figure of 3 out of 21 (with an "ablation" rate of 70%). More attention to the dose at the needle-holes should reduce this incidence further as is indicated in Fig. XV.3.
One technical difficulty in achieving precise dosage to the needle-holes

is the tendency for the rods to be sucked backwards as the implant needle is withdrawn, especially if the rod had not been pushed into unpenetrated pituitary tissue. Possibly this could be overcome by inserting a screw at the time of implantation; on first principles, it seems advantageous to avoid introducing a foreign body into the bone because, as shown in Chapter IV, actual ossification can occur in a few weeks, after which, even if there is a perforation through the diaphragma sellae, leakage could not occur.

Perusal of the literature shows that identical complications have been encountered by all the groups who have been implanting radioactive materials into the pituitary gland. As reviewed by Forrest (1959), implantation of gamma-emitting sources such as radon or Au-198 in the normal pituitary have not only failed to achieve ablation, but also have been accompanied by frequent chiasmal damage, and therefore these materials have been abandoned in favour of Y-90. By improvements in the accuracy of placement dependent upon a screw-mounted yttrium source, Forrest (personal communication, April 1963) has now reduced the incidence of C.S.F. rhinorrhoea to 8%, while there was over 90% necrosis in 88% of cases. When Forrest reviewed all the published series of implants in 1959, there was an overall incidence of C.S.F. leakage of 20%; in all series, the close connection between rhinorrhoea and meningitis was evident.

Complications from eight surgical series comprising 648 transcranial hypophysectomies for breast cancer were reviewed in 1960 (Kennedy et al., 1956; Andersson, 1958; Baron et al., 1958; Edelstyn et al., 1958; Luft et al., 1958; Cobb and Scoville, 1959; Ray and Pearson, 1958; 1959 and 1960; and Atkins et al., 1960). In some series, sclerosing or radioactive materials were put into the sella to ensure complete necrosis. Deaths attributed to the procedure were 6%, while total deaths in the first four weeks were 9%. An overall figure of 4% of patients sustaining some post-operative fits was obtained, but less severe seizures may be more common (Luft, 1957). Oculomotor pareses were only found in one series, where the Y-90 may have been responsible. Rhinorrhoea, usually transient, was reported in 14 cases,

and transient hemipareses in three. There were 33 instances of visual field loss or acuity loss out of 589 operations, but six were due to deliberate sacrifice of an optic nerve to facilitate exposure of the sella. Meningitis, re-opening for clots, and wound infection were rare occurrences. Figures were not usually given for permanent bilateral anosmia, but in three series amounted to about a third of the patients. Diabetes insipidus was common as a transient phenomenon, and possibly occurred in about a quarter as a permanent disability; this will become less common now it is appreciated that low section of the stalk carries a lower risk of this.

From a consideration of the above surgical figures, it would appear that the main disadvantages of transcranial surgical hypophysectomy, as compared with the needle implantation of yttrium-90 of the present study, were a slightly greater surgical mortality risk (6%) compared with 2% from Y-90, and the occurrence of fits and hemipareses; permanent diabetes insipidus was more common in the surgical series compared with 1% from the entire present series, although with current techniques, the incidence from both methods is very low. Similarly, with current techniques, visual defects are virtually unknown with both methode. On the other hand, the one serious complication of needle implantation, C.S.F. leakage, has yet to be overcome, while the risk of this in recent surgical series is negligible.

When the current results of hypophysectomy for breast cancer done by highly experienced neurosurgeons are compared with the current results of pituitary implantation, there is a slightly higher incidence of surgical mortality, fits and diabetes insipidus in the former, while there is still a definite risk of C.S.F. leakage in the latter. Fortunately, a leak can usually be arrested by simply inserting a stainless steel screw, and "meningitis" can be readily treated by antibiotics. Both methods seem effective in ablating the pituitary in the great majority of cases. An obvious advantage of needle implantation is that it is a relatively simple technique, and does not require the services of

a highly trained neurosurgical team; the patients can be ambulant a few hours after implantation, if their general condition permits.

When complications from transcranial surgical hypophysectomy for diabetic complications are considered quite a high risk of cerebral infarction is found (see Chapter XVI), so for this disorder, a trans-sphenoid approach or needle implantation have a clear superiority.

Because of an inevitable (although small) risk of damage to the optic chiasma, nerves, or tracts, and post-operative extradural clot compression, which attend the trans-cranial approach to the pituitary, Hamburger and his colleagues have revived the approach from below, via the maxillary antrum. An approach from below was probably first devised by Oscar Hirsch in 1910 for operations on tumours in this region using a trans-sphenoidal operation through the nasal septum. In 163 operations, Hamburger's group (1961) report that the procedure is now free from serious complications. Meningitis was originally a problem, but was later eliminated, and C.S.F. leakage which occasionally occurs has always ceased spontaneously in a short time. Diabetes insipidus occurred in most cases. With this trans-sphenoidal approach, an anatomical contra-indication has emerged. When pre-operative radiographs show that both sphenoidal sinuses are of the conchal type (3% of cases), it is not feasible to do a hypophysectomy by this route. More recently, Bateman has used a transethmoid approach, and Macbeth a transnasal osteoplastic approach. Results of the latter (Macbeth and Hall, 1962) from 36 operations gave an operative mortality of 2; C.S.F. leakage may necessitate re-operation to plug the dural defect. Reporting on his results, Bateman (1962) noted the following complications; haemorrhage in the pituitary fossa, C.S.F. rhinorrhoea requiring a second operation, and meningitis.

SUMMARY

1. The complications arising from Y-90 needle implantation for total pituitary ablation in 96 patients with advanced cancer (mainly breast) and 20 patients with diabetic retinopathy were described. Re-implantation was no more hazardous than the first implant.

2. C.S.F. rhinorrhoea was reduced by successive improvements in technique to the current figure of 3 in 21 (14%) Its occurrence after implants of two long Y-90 rods was shown to be associated with excessive irradiation, to above 300,000 rads, at both the needle-holes and diaphragma sellae.

3. The onset of C.S.F. rhinorrhoea was usually between the 12th and 72nd day, and when allowed to do so, it terminated spontaneously (6 patients) between the 56th and 210th post-operative days.

4. C.S.F. leakage was arrested by the insertion of a stainless steel screw in 5 out of 8 attempts.

5. Meningitis occurred in one third of the patients who had C.S.F. rhinorrhoea, and in all cases, subsided with antibiotics (especially chloramphenicol), usually quite rapidly. C.S.F. findings (other than culture) usually, but not always, confirmed the diagnosis of meningitis.

6. Oculomotor paresis was confined to the early operations, and could be attributed to the Y-90 seeds being too near the third nerve. This was shown by a method evolved for the measurement of seed-nerve distance using antero-posterior and lateral skull radiographs. Five of seven affected nerves had a seed placed within a distance of 3 mm., whereas only two of 43 unaffected nerves had a seed as close as this.

7. Optic chiasma damage was confined to the first few implants. It occurred in seven cases, and could always be attributed to a high

Y-90 seed, either at the normal radiological level of the diaphragma sellae, or above this. No patients with seeds as high as this failed to sustain this complication.

8. There were no deaths from omission or misjudged cortisone replacement therapy.

9. With the current implant technique, the only likely complication is C.S.F. leakage, and it is probable that this can be further reduced by avoidance of overdosage of excessive irradiation to the needle-holes.

PART IV

THE EFFECT OF PITUITARY IMPLANTATION ON DIABETIC RETINOPATHY, CUSHING'S DISEASE AND ACROMEGALY

CHAPTER XVI

THE EFFECT OF PITUITARY IMPLANTATION ON DIABETIC RETINOPATHY

Now that the principles of dietary treatment and insulin administration are well established, there is but little disturbance in the life of most diabetics - until they survive long enough to sustain the complications of the disease. Although there is no doubt that good diabetic control lessens the chance of development of complications (e.g. Hardin et al., 1956; Skouby, 1956), the diabetologist is virtually powerless to reverse the established complications of retinopathy, nephropathy, neuropathy, and accelerated vascular degeneration.

One of the most important complications is retinopathy. It is contributing an increasing number of blind registrations; for instance, 11.3% of blind registrations under the age of 60 in Great Britain in 1962 were due to diabetes mellitus. The liability to diabetic retinopathy is well correlated with duration of the disease. For example, in a study of 600 diabetics, Lundbaek (1963) quoted an incidence of 72% in those with diabetes for 15 to 25 years, and 93% in those with the disease for 25 to 35 years; 5% of the former and 17% of the latter had retinitis proliferans. 80% of cases with retinopathy showed progression over a 5 year period. Beetham (1963), from an extensive study of diabetic retinopathy concluded that the average time for transition from mild to extensive proliferating retinopathy was 5 years; however, a few of his patients had a spontaneous arrest. Caird (1964) from a detailed statistical study concluded that patients with good vision in both eyes and non-proliferative retinopathy develop economic blindness at about 5% per annum, those with growth-onset diabetes and proliferative retinopathy at 11% per annum, and those with maturity-onset diabetes and proliferative retinopathy at 25-30% per annum.

The immediate cause of diabetic retinopathy is totally unknown. It occurs both in "idiopathic" diabetes and (rarely) in pancreatic diabetes, such as haemochromatosis. Although abnormal venular dilatation has been found in the conjunctival vessels in most pre-diabetics (Camerini-Davalos et al., 1961), there is no record of

retinopathy visible ophthalmosoopically or by fluorescein photography before the oral glucose toleranoe test has become abnormal. It thus appears that retinopathy is in some way a consequence of frank diabetes.

Following the demonstration by Houssay and Biasotti (1930) that the anterior pituitary has a diabetogenic action in animal experiments, Luft and Olivecrona and colleagues commenced surgical hypophysectomy in 1951 as a likely means of arresting the progress of diabetic complications in man (Luft et al., 1955). This early work suggested that the retinal changes did not progress further in some cases after operation. Further support for the ameliorating effect of hypopituitarism on retinopathy came from the observation of Poulsen (1953) that the retinopathy of a diabetic underwent regression after sustaining post-partum hypopituitarism. Since these early reports, there have been a number of series reporting the effect of pituitary destruction on diabetic complications. From these, it emerges that the majority of cases with retinopathy have sustained some amelioration, while variable claims in improvement in other diabetic complioations have been made. However, surgical mortality, and morbidity have been rather high. Frontal lobe infarction appears especially liable in diabetios having a trans-cranial approach to the pituitary, due to the fragility of the cerebral vessels. Diabetes insipidus, which has been almost invariable in some series of surgical hypophysectomy, obviously presents a special problem to a diabetic.

It was because of a possible superiority of needle implantation of Y-90, in terms of a lesser surgical morbidity and mortality, that the present series was undertaken. The objective was to establish the degree of improvement in diabetic complications which might follow and to define the type of retinopathy most likely to respond. In this chapter, the results of implantation will be given. A total of 24 diabetics have been implanted; the degree of hypopituitarism and morbidity arising from the procedure will be based upon the whole series, but retinopathy progress will be analysed for only the 19

patients followed for over six months, 16 of whom could be followed by serial retinal photography. After the results of the first two years had shown some improvements, a non-implanted series was begun, and followed in the same way. The retinopathy progress of the implanted group can therefore be compared with this "control" group.

THE PATIENTS STUDIED AND METHODS OF ASSESSMENT

General plan of study.

At the first interview, a decision was made on the degree of urgency for implantation, based on reports of the rapidity of advance, and retinal appearance. "Urgent" cases were treated as soon as arrangements could be made, in which case the only pre-implant observations and photography were at the first out-patient visit, and again in the few days of in-patient observations just before implantation. "Non-urgent" cases were seen monthly, for three photographic assessments, before implantation.

Following implantation, most of the patients were at first examined three-monthly and then six-monthly. Most attended their own diabetic clinics for routine diabetic control. At each assessment, a full clinical examination was carried out, and was supplemented by retinal photography, and various urine and blood tests. In addition, specialist ophthalmological measurement of visual acuity were made.

The series began with the implantation of case C. Br. in October 1959. Up to the implantation of case C.Hi. in September 1961, 15 patients had been treated by implantation and four "control" cases had been followed. All had been personally assessed and supervised, and nearly all the serial retinal photography had been done by the writer up to this time. After this, the immediate patient care and retinal photography was transferred to my colleagues, and 12 further "control" patients were added, by randomisation.

Indications for implantation

These were deliberately rather wide in this initial series, so as to introduce a minimum of selection.

1. The patient must have definite disability from loss of vision in one or both eyes, due to diabetic retinopathy.
2. There must be a reasonably healthy area of retina visible in one eye (This was not adhered to in three cases).
3. The blood urea must be under 70 mg.%

4. The patient's cooperation must be adequate for the management of replacement therapy.

The patients who were implanted.

A total of 24 diabetics had been implanted, as treatment of diabetic retinopathy, up to 15/3/63. Only one patient was from the Hammersmith Hospital Diabetic Clinic, at which there are about 600 attenders. The remainder were referred specifically for consideration of implantation. In one further patient (case Z.Mo. - see Chapter III, page 80) implantation could not be done, owing to the emergence of C.S.F. down the implant needle as soon as the fossa was entered (in correct position). A screw was inserted and the procedure abandoned. No ophthalmic follow-up was obtained.

Table XVI.I shows the age, sex, duration of diabetes since diagnosis, and other complications present in the 19 patients whose retinopathy had been followed (16 by photography) for over 6 months.

TABLE XVI.I.

19 PATIENTS WITH POST-IMPLANT RETINOPATHY DATA

Age	Sex	Duration of D.M. (years)	No. on insulin	>5 yrs. neglect	Diastol. B.P. >100mmHg	Protein-uria >1G/d.	Blood urea >50mg%	Neuro-pathy present
24-64 (38)	16M 3F	1-34 (18)	17	4	9	11	4	18

The patients who were not implanted

A total of 16 non-implanted patients with diabetic retinopathy were followed by serial retinal photography for three to 30 months on optimum medical management. Their photographs were assessed in the same manner as the implanted group. The group comprised nine patients serially studied for at least three months before implantation, (i.e."non-urgent" cases), three patients assigned to the untreated

control group by random selection, two patients who were offered operation but declined it, and two other patients with fairly severe retinopathy in whom photography had been undertaken initially for another reason. Clinical details of this group are shown in Table XVI.II.

TABLE XVI.II.

16 UNIMPLANTED PATIENTS FOLLOWED AS A CONTROL SERIES

Assessment before commencing serial study

Age	Sex	Duration of D.M. (years)	No.on insulin	>5 years neglect	Diastol. B.P.>100 mm.Hg.	Protein->1G/d.	Blood urea >50mg%	Neuropathy present
25-63 (42)	13M 3F	1-26 (13)	11	5	7	7	1	13

Procedure for retinal photography

All the retinal photographs was done on a Zeiss retinal camera, using Kodachrome film; colour transparencies were thus produced, ready for examination on a projector.

On each occasion a patient underwent photography, the following areas of each retina were routinely photographed: first, pictures were taken centred on the disc and on the macula, and then a ring of pictures were taken around the disc, at 45 degree intervals, each centred so that the disc edge was just included in the field. Such a ring of photographs were eight in number, and overlapped sufficiently to provide two photographs of most of the central retinal territory, 30° around the disc. In addition, extra photographs were taken of the more peripheral retina to show particular lesions, or focussed specially on retinitis proliferans to show its vascular detail in cases where this tissue projected forwards into the vitreous.

Method of assessment of the retinal photographs

(a) Inspection of photographs.

Two similar projectors were used, arranged to throw images of

about one foot in diameter side by side on the screen. For each patient, photographs had been taken (see above) on a number of occasions, to document the retinal progress. The method of inspection of the photographs for a given patient, was to follow the progress of one field at a time. Thus, for a particular field, there might be six photographs taken over a 2-year interval period. The procedure would then be to compare the serial photographs, by comparing them in pairs, using the pair of projectors. The first would be compared with the second, the second with the third, and so on. In all cases, the examinations were made initially independently by three observers (DJ.S., D.W.H., and G.F.J.) and where opinion about any change differed, they were resolved by discussion. It was arranged that two observers were in ignorance of chronological order of the pair of pictures.

It was usually found that about six fields, covering territories in both eyes, were available for serial study in each patient.

(b) Criteria for recording change in retinopathy.

When each pair of photos was examined, record was made of change in each of the following components separately: retinal haemorrhages, new vessel formation in the retina, venous dilatation, exudate, and retinitis proliferans. These components will now be considered further.

Retinal haemorrhages. Microaneurysms were included as "haemorrhages" because of the difficulty in distinguishing them from tiny haemorrhages. A claim of change was based on change in number of separate haemorrhages, rather than area of retina covered with blood.

Venous dilatation. Two different appearances were considered. Diffuse dilatation of a vein was only recorded as abnormal if its caliber diminished as it ran from the periphery towards the disc. Localised dilatation was more definite, often taking the form of a number of dilated segments along the course of the vessel. Change in caliber near the disc or arterio-venous crossings were disregarded as these may occur in normal eyes. Change in venous dilatation was recorded when the calibre of an abnormal segment altered, or a new lesion appeared.

New vessel formations. Only abnormal vessels in the retina itself were considered. They could usually be identified as abnormal by their course and calibre being abnormal, and their tortuosity.

Exudate. Only hard exudate was considered. A change was recorded if there was alteration in the total area of retina involved.

Retinitis proliferans. Under this heading was considered the extent of gliosis, irrespective of whether it appeared to be on the retina, or projecting forwards into the vitreous.

Recording was done by assigning one to three plusses to the extent of each type of lesion, in each field, at each date that photographs had been taken. A "one plus" abnormality implies that minor lesion is present, "two plus" that the lesion is moderately extensive, and "three plus" that the abnormality is gross. Because the number of fields available for study had varied from patient to patient, and in the same patient from time to time (e.g. temporary obscuring by vitreous haemorrhage), change in a given component of the retinopathy was recorded as the mean change (in plusses) per field. If this figure exceeded 0.33 for example, the implication is that a change of one plus occurred in one of three fields, or in two of six fields. Only a change of 0.33 or more was recorded for compiling the results (Table XVI.III and XVI.IV.)

Assessment of visual acuity.

Corrected visual acuity was measured periodically (Snellin) by D.W.H. For the purpose of recording progress, corrected visual acuity in the better eye was graded as normal (6/5 6/6), slightly impaired (6/9 6/12), moderately impaired (6/18 to 6/60) and severely impaired ($< 6/60$). A change was recorded when the acuity changed from one grade to another.

Other complications and parameters of diabetes studied.

Neuropathy was followed clinically.

Nephropathy was indexed by serial measurements of the protein content of a 24-hour urine collection, and the blood urea.

Insulin requirement was quoted as the dose which would give good control, based on six urine tests daily for in-patients, and three tests daily as out-patients, supplemented by blood sugars as available.

Patient management for pituitary implantation

Patients were usually admitted a week before implantation and placed on their accustomed out-patient diet. This was to enable diabetic control to be achieved, and hence the insulin requirement ascertained while pituitary function tests and measurement of proteinuria were done.

For the first two years, the only steroid cover administered was cortisone 12.5mg. 6-hourly, commencing just before the operation, but when it was realised that the diabetics were sometimes notably lethargic, nauseated, and had more headache when compared with patients with breast cancer having an identical implant, the dose of steroid was raised to give 300mg. cortisone intravenously during the first 24 hours, and then prednisone in a dose of 10mg. 4 hourly for five days, when the dose was reduced to a maintenance level. This greatly reduced the incidence and severity of post-operative nausea and headache. Initially, steroid withdrawal was done routinely, as with the breast cancer cases, after the 10th day, as part of the assessment of adequacy of the implant, but the consequent disturbance to diabetic control and difficulty in doing a W.D.T. was found to be too great to justify this as a routine.

Those patients requiring insulin required special attention to avoid hypoglycaemia. It was found that the insulin requirement usually dropped precipitously on the fifth post-operative day, so in anticipation of this, the dose was routinely halved on that day.

Antibiotic cover with streptomycin and sulphadiazine was given routinely for the first five days.

The dose plan of Y-90 implantation.

At first, five patients had implants of multiple short (3mm) seeds of Y-90, each planned to give the gland surface 100,000 rads.

The remaining 19 patients had two long rods implanted, whose

length was adjusted according to the fossa length, and activity according to the dose required at the diaphragma sellae. It was planned to give the diaphragma sellae 100,000 to 150,000 rads to four patients, and 300,000 rads to 15 patients.

RESULTS

The effect of pituitary implantation on diabetic retinopathy as shown by serial retinal photography and compared with a non-implanted series (Tables XVI.III and XVI.IV).

The change in the retinal photographs in the 16 patients who were followed for 6 to 38 months after implantation are shown, irrespective of the degree of hypopituitarism induced, in Table XVI.III. Their results can be compared with the results of the 16 non-implanted patients followed for 3 to 36 months, in Table XVI.IV. "Unassessed" patients in these two tables were those whose serial photographs were incomplete, usually due to intercurrent vitreous haemorrhages or haze, but sometimes due to technically inferior photographs.

The two series should first be compared with respect to the extent of retinopathy present at the beginning of study: haemorrhages were present in every patient of both series and each of the other retinopathy components were present in over two thirds of the patients in the implanted series and also in the non-implanted series. There was a slightly greater proportion of abnormal components in the implanted series.

It can be seen from inspection of Tables XVI.III and XVI.IV that "better" was recorded in just one instance (haemorrhage) in the non-implanted group; in contrast, "better" was recorded in the majority of implanted patients with respect to haemorrhages (8/12) and new vessels (6/8), and in some patients for venous dilatation (3/8). This would seem to be a clear difference between the two groups. An example of reduction in the number of retinal haemorrhages and reduction in venous dilatation is shown in Fig. XVI.I.

Although exudate was only found to improve in one out of seven patients after implantation, deterioration only occurred in 1; in contrast, six out of 11 non-implanted patients deteriorated.

It is manifest that retinitis proliferans was unimproved by operation, and probably entirely uninfluenced.

TABLE XVI.III

IMPLANTED GROUP.

CHANGE* IN DIABETIC RETINOPATHY IN 16 PATIENTS FOLLOWED FOR 6 to 38 MONTHS AFTER PITUITARY IMPLANTATION

	Better	No change	Worse	No abnormality	Unassessed
Haemorrhages	8/12	4/12	0/12	0	4
New vessels	6/8	2/8	0/8	3	5
Venous dilatation	3/8	5/8	0/8	2	6
Exudates	1/7	5/7	1/7	5	4
Retinitis proliferans	0/13	6/13	7/13	2	1

TABLE XVI.IV.

NON-IMPLANTED GROUP

CHANGE * IN DIABETIC RETINOPATHY IN 16 PATIENTS FOLLOWED FOR 3 to 30 MONTHS

	Better	No change	Worse	No abnormality	Unassessed
Haemorrhages	1/16	13/16	2/16	0	0
New vessels	0/10	8/10	2/10	6	0
Venous dilatation	0/11	10/11	1/11	4	1
Exudates	0/11	5/11	6/11	3	2
Retinitis proliferans	0/10	8/10	2/10	6	0

* "Change" in each retinopathy component is shown as the proportion of patients assessable as better, unchanged, or worse.

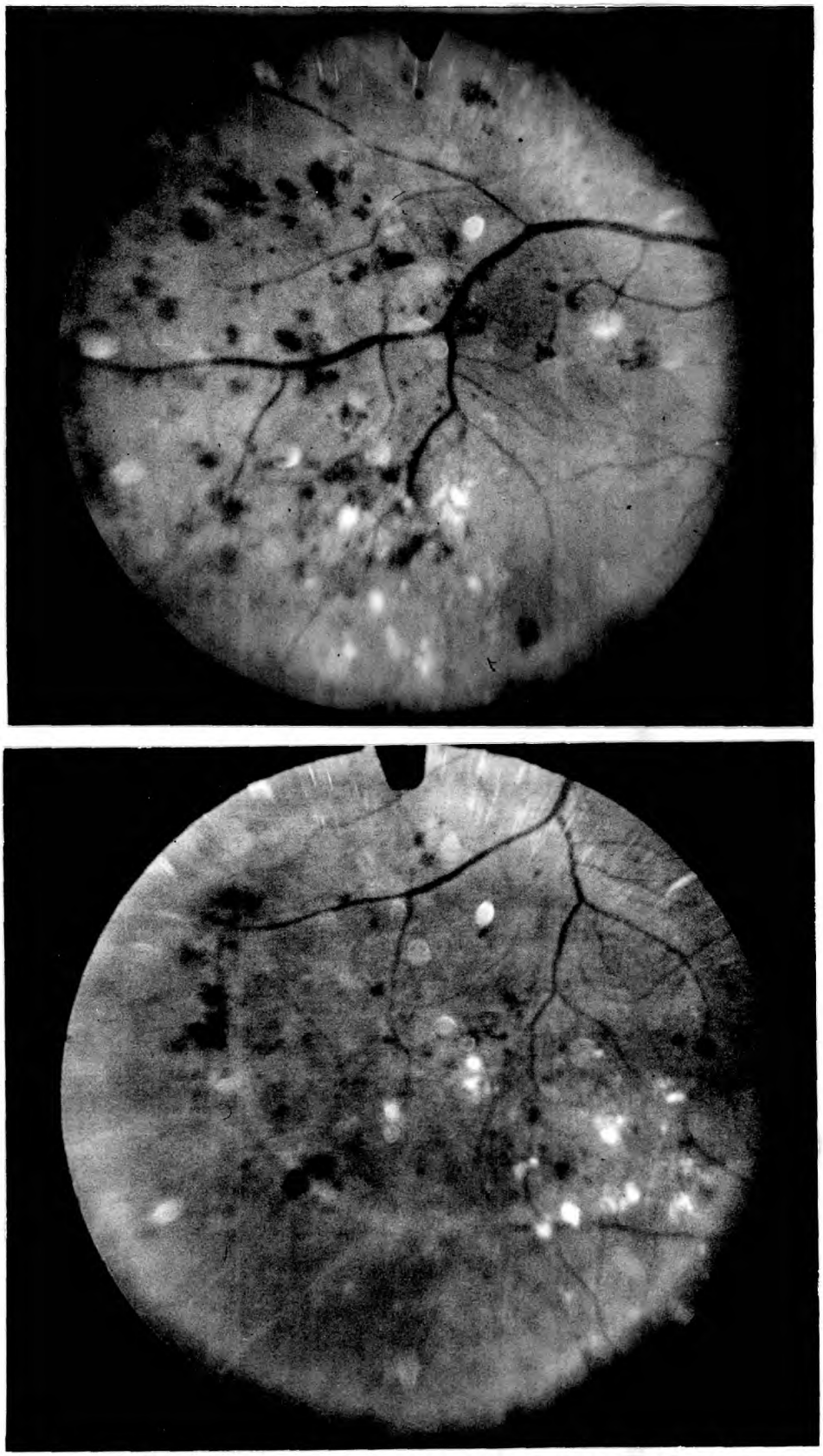


Fig.XVI.I. This is a right superior temporal field before and 6 months after implantation. There is a reduction in retinal haemorrhages, and the venous dilatation is less. Exudates are unchanged. (Monochrome prints from 'Kodachrome' transparencies).

The usual time after operation at which improvements first occurred in haemorrhages, new vessels and venous dilatation was about six months, and improvement continued to occur thereafter in some.

The effect of pituitary implantation on the frequency of vitreous haemorrhages

Eight implanted patients followed up for 12 to 36 months gave a history of vitreous haemorrhages before implantation. There were nine seeing eyes involved altogether. There was considerable variation in the progress of these eyes after implantation; some showed complete cessation of vitreous haemorrhages, and others continued at about the same annual rate. None showed a significant increase. In view of the variability in the natural history of vitreous haemorrhages, and poor memory of many patients about the occurrence of the episode, it is not possible to assert that implantation has materially affected the frequency of vitreous haemorrhage, but it might have done so.

The effect of pituitary implantation on visual acuity.

19 implanted patients were followed for 6 to 36 months, and 11 non-implanted patients were followed from 6 to 30 months. At the commencement of study, the acuity impairment of the two groups was comparable.

The results are summarised in Table XVI.V (a), as at the end of the first year and (b) at the end of the second year. A change was recorded when the acuity of the patient's better eye changed from one grade to another. The numbers of patients are insufficient to give a clear comparison of the progress of the implanted and non-implanted groups, but there is a tendency for worsening to be less frequent in the implanted group.

TABLE XVI.V

CHANGE IN VISUAL ACUITY OF THE BETTER EYE IN IMPLANTED AND NON-IMPLANTED PATIENTS

	Improved		Unchanged		Worse	
	At 12 mths	At 24 mths	At 12 mths	At 24 mths	At 12 mths	At 24 mths
Implanted	5/15	1/6	8/15	3/6	2/15	2/6
Not implanted	1/5	0/2	2/5	0/2	2/5	2/2

Comparison of retinopathy results in partial and complete ablation

When the implanted patients were divided into two groups according to their endocrine function tests (see later), the frequency of response of the various retinopathy components could be compared.

The effect of "partial" ablation was as follows. Four patients were followed with respect to haemorrhages; three showed improvement and one showed no change. New vessels improved in two and remained unchanged in two; venous dilatation improved in one and was unchanged in one, and exudate improved in one and was unchanged in one. It is thus evident that although the numbers of partially ablated patients followed is small, there is no doubt that they can respond to operation; greater numbers may demonstrate a lessened likelihood to respond, and a longer follow-up may show a difference in their maintaining their response. There is no general trend for pituitary function to subsequently improve in the partially ablated patients (see Chapter VII).

Effect of implantation on neuropathy and nephropathy.

Neuropathy was assessed clinically by noting change in the knee and ankle jerks, and extent of loss of sensation to vibration, cotton wool and pinprick. Nineteen implanted patients were followed up for 6 to 36 months. Eighteen had some abnormality at implantation, and one was normal. There was no patient showing any improvement, while seven deteriorated, two very strikingly.

Proteinuria was followed quantitatively for a year or more in nine patients after implantation; three had no proteinuria before implantation, and still had none at the last assessment; three had over 5 grams per day pre-operatively, and all showed reductions (which were of 3, 3 and 5 grams per day), and there were three patients with proteinuria of under 5 grams per 24 hours and all showed small reductions. The blood urea was followed for over a year in 13 patients. All were initially under 50 mg%. There were no significant alterations, with the exception of one patient showing a rise from 35mg% to 67mg%. An additional patient (case D.Fo.) followed for less than a year died

12 months after partial pituitary ablation, of relentless progression of nephropathy. At the time of implantation the blood urea was 56mg%, blood pressure 175/100, and there was proteinuria of 14 gm/day. Over the next year the blood urea steadily climbed and severe oedema developed.

There was no trend for blood pressure to rise or fall after implantation, apart from the patients with postural hypotension.

Effect of pituitary implantation on the diabetes.

There was no instance of a patient losing the disease after implantation, although two patients were able to obtain control by replacing insulin with tablets or diet alone.

In seventeen patients, the insulin requirement was established before implantation and again after implantation on replacement therapy. In every case, the insulin requirement fell. In the nine patients with "total" ablation the fall was by 27% to 92% (mean 54%); in the eight patients with but "partial" ablation, the fall was by 24% to 76% (mean 46%).

Diabetic control was assessed in 19 patients. It was found easier in 4, more difficult in 1, and unchanged in the remaining 14. However, hypoglycaemic episodes tended to be more frequent, and required more care in their management; in no patient did this constitute a problem, once they became familiar with their increased sensitivity to insulin.

Endocrine effect of implantation.

For the purpose of classifying the diabetics into a group whose pituitary was "ablated", and a group with but "partial" ablation, the criteria for "ablated" were taken as a 48-hour neck uptake of I-131 of <21%, as well as steroid dependency (if tested). On this basis, the 19 implanted patients whose retinopathy progress was reported were divided into "ablated" and 9 "partially" ablated cases.

The effect of implantation in this series will now be detailed according to the planned dose to the diaphragma sellae.

100,000 to150,000 rads. Nine patients were assessed by means of a 48-hour I-131 uptake at least 14 days after implant. Three were under 21%; two of these were further followed, and found to be steroid dependent, and became clinically myxoedematous. Of the six with a neck uptake of over 20%, one whose value was 29% became clinically myxoedematous with a typical E.C.G. change, and was also shown to be clinically steroid dependent on the 10th day of steroid withdrawal.
300,000 rads. Thirteen patients were assessed. The 48-hour I-131 uptake was under 21% in nine, of whom eight were subsequently followed and became clinically myxoedematous. Four patients had an I-131 uptake over 20% but two whose tests were 30% and 35% became myxoedematous with a supporting E.C.G., and one was tested by steroid withdrawal and found to be clearly steroid dependent.

The serum cholesterol was measured three months post-operatively in six patients whose I-131 uptake was under 21%; five showed a rise from a normal level to above the upper limit of normal (324mg%), and all that were re-checked after commencement of thyroxine fell to normal again. In three out of nine patients whose I-131 neck uptake was over 20%, the serum cholesterol at three months rose to an abnormal level.

The complications of Y-90 pituitary implantation, and causes of death in the series.

A total of 24 diabetics had been implanted up to 15/3/63. There were four instances of C.S.F. rhinorrhoea; three settled spontaneously and one after the insertion of two screws. There were four patients who sustained an attack of what appeared clinically to be meningitis. Three in whom C.S.F. rhinorrhoea had occurred, had a sterile C.S.F. and responded to antibiotics; the fourth died of pneumococcal meningitis, unassociated with a C.S.F. leak, three months after implantation.

There have been five additional deaths, occurring eight weeks to 15 months after implantation. One was due to mismanagement of a hypoglycaemic attack and one (case C.Hi.) was due to an electrolyte disturbance arising during the treatment of severe postural hypotension. There were two deaths from myocardial infarction, and one from progression

of severe diabetic nephropathy, all at about one year after operation.

Postural hypotension was present pre-operatively in case C.Hi. producing but occasional symptoms. Post-operatively it became very much worse. One other patient sustained temporary disability post-operatively but later spontaneously improved.

DISCUSSION

The main feature which has been studied is the effect of implantation on the retinopathy. It seems clear that this can be favourably influenced in half to two thirds of patients with respect to retinal haemorrhage, new vessel formation, and venous dilatation, but doubtfully with exudate, and not at all with established proliferans. Improvement can be anticipated at six months. By comparison, the progress of the non-implanted group treated by optimum medical management was conspicuously worse, and as the two groups initially had comparable retinopathy, and were similarly constituted with respect to the general medical background, there is little doubt that the procedure can have a distinct ameliorating effect on the appearance of the retinopathy.

From a survey of the literature to March 1962, a total of 18 patients in five series had been treated with surgical hypophysectomy or stalk section, and the retinopathy followed up for over a year (Luft et al.,1955; Kinsell,1957; Hernberg et al.,1959; Ray,1960; Field et al., 1961); 12 patients were claimed to be improved, and five stationary. The methods for these assessments varied widely, some being precise, and others rather subjective. The only series followed with retinal photography and reported in detail, comparable to the present series was that of Hernberg and his colleagues (1959). Here, striking improvement was noted in retinal haemorrhage and venous abnormality, as was seen in the present study. But 7 of 8 eyes showed an actual improvement in exudate, and one of seven cases of retinitis proliferans improved.

A total of 72 surgical hypophysectomies or stalk sections for diabetic retinopathy have been reported in eight series from which morbidity and mortality could be obtained (the above five series with the addition of Moore, 1957; Slater and Nabarro, 1958; Javid et al., 1958). There were a total of seven immediate post-operative deaths attributed directly to surgery, i.e. 10%. Six further patients died as a consequence of hypoglycaemic episodes, and eight from advancing renal disease. Difficulty in the surgical approach to the pituitary led to

the deliberate severence of the optic nerve of the worse eye in some cases. Direct surgical morbidity and mortality was thus quite substantial. No doubt it will be reduced when more experience is gained, and retraction of the frontal lobe can be avoided, as the brittle cerebral vessels withstand manipulation poorly (Luft, 1962); extracranial approaches to the pituitary would also avoid this risk. It would appear that the advantage of Y-90 needle implantation lies in the avoidance of direct surgical mortality; its only complication was C.S.F. leakage and consequent risk of infection. There was a single death from this cause among 24 implants.

Because of the surgical risks, some centres have been trying external irradiation of the pituitary, but it is clear that severe hypopituitarism cannot be achieved safely in this way. However, slight diminution of pituitary function can be induced without risk with about 12,000 rads delivered by proton beam, and some instances of improvement in retinopathy have been recorded (J.H.Lawrence, 1962; photographic evidence inspected by the writer).

The important question of whether total pituitary destruction is required for best results, or whether partial destruction is sufficient is still to be conclusively shown. Both in the present series, and in the literature, good results have been obtained by partial ablation, for example by stalk section or external irradiation. A controlled series is awaited to answer the question of the comparative effectiveness of partial and complete ablation, both with respect to the frequency of good response, and its duration.

The effect of pituitary destruction on visual acuity is less easy to ascertain than the changes induced in the retina. This is largely due to the fluctuation in vision due to intercurrent vitreous haemorrhage, fortuitous encroachment upon the macula of the various retinal lesions, and mechanical factors such as detachment. It is therefore necessary to have much larger numbers of patients and longer periods of follow-up to evaluate the effect on vision, so as to validly compare the results in the treated and control groups. However, in the present series, there is already a hint that preservation of vision is occurring, and

this has been claimed by many of the other authors quoted above.

With respect to hard white exudate it is to be noted that PAS treatment, and lowering of the serum cholesterol level may effect clearing, as illustrated by the series of Esmann et al., (1963).

It is difficult to ascertain whether pituitary implantation had a beneficial effect upon the nephropathy. One patient with heavy proteinuria and a mild elevation of blood urea at the time of implantation continued to deteriorate and died nearly a year later. On the other hand, this was the only patient who did show significant renal deterioration; the remainder remained unchanged, or even achieved reduced proteinuria. Hernberg and colleagues (1959)also noted improvement in proteinuria in some cases, and no deterioration in creatinine clearance, and this would seem representative of the experience of the other authors.

Neuropathy has clearly continued to advance in the present series, probably unmodified by pituitary implantation. Reports on change in neuropathy are too few in the literature to provide a comparison. Postural hypotension is well recognised as an occasional problem in these severe diabetics after pituitary destruction. In the present series, this indirectly led to a death. Presumably a pre-existing autonomic neuropathy of sufficient severity to cause moderate symptoms before implantation can cause severe symptoms post-operatively if slight sodium depletion or diabetes insipidus should occur; perhaps an aggravation of the neuropathy can also occur as a consequence of severe hypoglycaemic episodes, which in fact were a feature of the post-operative course in case C.Hi, because sodium repletion and fludrocortisol failed to correct his condition. It is clear that pituitary destruction should not be done in such patients.

The explanation for the response of diabetic retinopathy to pituitary ablation is speculative. One possibility is that it is simply a consequence of better diabetic control. There can be little doubt that liability to retinopathy is to a certain extent related to the adequacy of diabetic control (Wilson et al., 1951; Skouby, 1956; Paul and Presley, 1958). The study of Skouby (1956) showed that when a population of 286 diabetics were randomly assigned to one of two

types of diet, one strict and associated with good diabetic control, and one fairly free, and associated with poor control, the patients with the stricter type of diet sustained fewer complications. In the present study, it was noted that amongst the total of 35 patients with severe retinopathy, nine admitted to having neglected their disease for over five years. When this incidence of 25% of patients with severe retinopathy having seriously neglected their disease is considered in the light of their control having invariably become excellent when their serious complications became evident, there can be little doubt that poor control was a contributory cause of the advanced complications; severe retinopathy was not just an association with a brittle type of disease as there were no such cases. However, the above consideration of diabetic control was only related to the evolution of complications, and is not related necessarily to arrest or regression of retinopathy. There is little evidence in the literature about the effect of instituting better diabetic control on the progress of established retinopathy. From the study of the non-implanted patients in the present study, the only instance of improvement in retinopathy with the institution of maximum diabetic control was in haemorrhages; a small number of similar improvements was also found by Dr.W.P.Beetham (personal communication) at the Joslin Clinic. However, in adults, regression of new vessel formation has not been shown as a consequence of improved control. It therefore appears that there is a favourable effect of pituitary ablation upon diabetic retinopathy, over and above any improvement in diabetic control.

This leaves endocrine factors for consideration. As cortisone and thyroxine are routinely given to patients after pituitary ablation, in amounts to assure normal health, it would appear most unlikely that a fall in adrenal cortical * or thyroid function are relevant, thus leaving a drop in growth hormone output as a possibility. The great

* Although occasional claims have been made for improvement in diabetic retinopathy following adrenalectomy (Green et al., 1950; Becker, 1957), the good response to stalk section in the patient of Lourie et al., (1962)points to the greater hypophyseal influence.

sensitivity to growth hormone of hypophysectomised diabetics has been well demonstrated (Luft et al.,1959; Hernberg, 1960), and underlines the strong connection between growth hormone and the diabetic state, although proves no relationship with complications. In this connection, the finding of Ensinck and Vallence-Owen (1963) that a polypeptide called "synalbumin" is present in abnormally high concentration in the plasma of all essential diabetics and that its presence is dependent on an intact pituitary, is of considerable interest. It is conceivable that this compound is a permissive factor in the development of diabetic retinopathy, at least at the early stage of retinal capillary closure and capillary dilatation which is probably ultimately responsible for the haemorrhages and new vessel formation seen clinically.

Pathogenesis of diabetic retinopathy

There are two theories currently in vogue.

The "shunt thesis" of Cogan and Kuwabarra (1963) is that the primary defect is a loss of the mural cells of some retinal capillaries, and that this allows them to dilate and to form microaneurysms and to undergo endothelial cell proliferation. These workers hold that once these dilated channels are constituted, they attract the major portion of the capillary circulation, and thus the adjacent unaffected capillaries are not perfused, and therefore close. Other manifestations of diabetic retinopathy then follow. When the regression of diabetic retinopathy is considered in the light of this theory of pathogenesis, it is difficult to see how hypophysectomy could restore the mural cells to the abnormal vessels and thus cause their resumption of a normal caliber and permeability.

An alternative pathogenesis has been proposed by Ashton (1963). On his theory, the areas of capillary closure are thought to be caused by impairment of their blood supply, possibly due to gradual occlusion of the relevant terminal arteriole. As a consequence of the ischaemia, the capillaries adjacent to this area dilate and show tortuosity, endothelial proliferation, and microaneurysms which are so characteristic

of the diabetic retina. Ashton emphasises that endothelial proliferation and microaneurysm formation are a consequence of retinal ischaemia, irrespective of its cause. Furthermore, the microaneurysms arising from a defect in the capillary basement membrane, are not unique in any way to diabetes; the lipoid and hyaline infiltration seen around the microaneurysm in diabetes is similar to that seen in hypertension, venous thrombosis, or macroglobulinaemia and they are considered to be a non-specific consequence of abnormal basement membrane permeability. The abnormal and often tortuous vessels in the diabetic retina are probably abnormally fragile, and liable to haemorrhage; intravenous injections of fluorescein have been commonly found to show their abnormal permeability (Scott et al.,1963) and hence the other features of retinopathy appear. Now if the consequences of capillary closure were ameliorated, the stimulus (on Ashton's theory) for capillary dilatation, and sequelae would be removed. In other words, the present author's postulate is that in diabetics pituitary destruction slightly but significantly diminishes the requirement of retinal tissue for a blood supply. Perhaps the abolition of Vallance-Owen's insulin antagonist or growth hormone itself is the mechanism.

Conclusion

The ideal stage of retinopathy for implantation is when the disease has already produced some disability in one eye, and hence intervention is justified in the patient's mind. There should not be exudate encroaching on the macula of both eyes, as visual loss cannot return then; also, there should be a minimum of retinitis proliferans, and certainly none near enough to the macula of both eyes to threaten vision for mechanical reasons. Positive indications are numerous retinal haemorrhages, and areas of new-vessel formation on the retina, and venous abnormality, as these are susceptible to improvement. Ideally, the blood urea should be normal; the poor prognosis of severe nephropathy makes ablation unjustifiable in such cases. Significant postural hypotension is a further contraindication. Average intelligence is required for the patient to manage the insulin sensitivity and replacement therapy.

SUMMARY

1. By serial retinal photography in 16 diabetics followed for 6 to 38 months after Y-90 pituitary implantation, it has been found that reduction in retinal haemorrhage occurred in 8 of 12 patients, regression of new vessels on the retina occurred in 6 of 8, and reduction in abnormal venous dilatation occurred in 3 of 8. Hard exudate diminished in 1 of 7, but no regression of retinitis proliferans was seen in 13 patients. It was not possible to show a clear effect on the frequency of vitreous haemorrhage or visual acuity.

2. Similar serial photography was assessed in 16 non-implanted diabetics treated by optimal medical control, whose general medical status and retinopathy were comparable to the implanted group. In a follow-up from 3 to 30 months, the only regression noted was an improvement in haemorrhages in a single patient. Exudate increased in 6 of 11 patients, in contrast to 1 of 7 implanted patients.

3. Some of the implanted patients sustained severe hypopituitarism, and others but partial ablation, as shown by endocrine function tests. Some patients with but partial ablation obtained good retinopathy responses, but the number of cases and duration of study do not permit conclusions about the respective effectiveness of partial and "complete" ablation.

4. In 9 implanted patients followed for over a year proteinuria remained unchanged or slightly diminished; blood urea similarly remained unchanged in all 13 patients followed over one year. A single patient showed continued renal deterioration, and died from this within 12 months.

5. Neuropathy continued to deteriorate in many patients, and appeared uninfluenced by implantation.

6. Complications of implantation in 24 cases comprised 4 instances of C.S.F. rhinorrhoea, one of which failed to cease spontaneously and was arrested by insertion of screws. There were three patients who had an attack of what clinically appeared to be meningitis with a sterile C.S.F: all responded to antibiotics. A fourth

patient in whom the C.S.F. was infected failed to respond to treatment and is the only patient whose death was attributable to the surgical procedure.

7. There have been a total of 6 deaths in the implanted group, all being after the 8th week: meningitis (1), postural hypotension (1), hypoglycaemia (1), nephropathy (1) and myocardial infarction (2).

CHAPTER XVII

THE EFFECT OF PITUITARY IMPLANTATION ON CUSHING'S DISEASE

The treatment of Cushing's syndrome (adrenocortical hyperfunction with respect to cortisol oversecretion) when due to an adrenal tumour is undisputably by surgical excision. This leads to a complete and permanent disease remission, and is uncomplicated by subsequent formation of a pituitary tumour (Sprague et al., 1961).

On the other hand, when the abnormally high cortisol secretion rate is due to bilateral adrenal cortical hyperfunction without tumour (often termed adrenal hyperplasia, although architectural hyperplasia is not always present), conventional therapy is far less satisfactory. This condition, which is sometimes known as Cushing's disease isusually treated by surgical excision of the adrenals, partial or total. However, it has occasionally been treated by direct radio therapeutic or surgical attack on the pituitary. External pituitary irradiation has undoubtedly yielded some remissions, but these have often been but partial or temporary. Pituitary surgery has been but infrequently attempted, partly due to the risk of the operation and of hypopituitarism, and partly due to the concept (e.g. Horwith and Stokes, 1960) that Cushing's disease is primarily a disease of the adrenals rather than arising from the pituitary. The results of the reported series will be considered later. It is interesting that Cushing himself considered this to be a pituitary disease, and in 1932 he rsported a remission in one of his patients treated by a small dose of external irradiation. An extension of this type of therapy was the implantation of radon seeds into ths pituitary at craniotomy by Pattison and Swan (1938) and Northfield (1949). Dissase remissions were obtained without hypopituitarism.

The current vogue (Sprague et al., 1961) is to treat this condition more and more by total rather than by subtotal adrenalectomy. This is because of the risk of disease recurrence with the latter, unless the excision is so radical that hypoadrenalism is commonly induced (see later). A special sequsl has emerged following adrenal excision. About 10% of patients have, or subsequently develop pituitary tumours (Jailer and

Holub, 1960), which may reach sufficient size to necessitate neurosurgery, or even become malignant. Of course, the operation of bilateral adrenalectomy itself presents risks to these patients who are often rather ill.

Because of the inadequate effect often achieved by external pituitary irradiation, and disadvantage of adrenal surgery with respect either to risking recurrence after subtotal adrenalectomy or causing Addison's disease, the present series was undertaken. The objective was to ascertain the effect which could be obtained by a dose of interstitial irradiation, which would be small enough to avoid panhypopituitarism, yet adequate to suppress the hypersecretion of ACTH which is now believed to be the usual cause of the condition. In this way, not only might hormone dependency be avoided, but also there might be a diminished risk of pituitary tumour growth.

The prospect of treating those patients whose Cushing's syndrome is due to adrenal hyperplasia by pituitary destruction rather than by adrenal surgery makes the accurate pre-operative assessment a practical pre-requisite. Hence the tests used to make this initial assessment will be specially considered in this chapter, as well as the results obtained by pituitary implantation.

THE PATIENTS TREATED AND METHODS USED

The patients treated

A total of 13 patients were treated by pituitary implantation for Cushing's syndrome of various etiologies. Their ages at implantation were from 11 to 72 years, the mean age being 37 years. Apart from two children, both of 11 years, all were over 25 years of age. There were 3 males and 10 females. The first operation for Cushing 's syndrome was on 4/5/59, and the last in this series was on 26/6/62.

Previous (ineffective) treatment had been given to two patients; one (case H.Ne.) had had an adrenal adenoma removed, and the other (case S.Sa.) had already had a large amount of malignant adrenal tissue removed.

Corticosteroid measurements.

Basal urinary 17-KGS (Chapter VIII), being the mean of at least two consecutive 24-hour collections, were invariably made. Values above 18 mg./24hrs. are abnormal. In addition, two elaborations were used:

(a) Dexamethasone suppression test. Dexamethasone was administered orally in a dose of 1 mg. 6-hourly for 5 to 7 days, 24-hour collections being made on the last two days. Normal subjects show suppression to 4mg./24hrs. and below (Slater et al., 1962). Later, shorter periods of dexamethasone administration were used; results of such tests will be specially identified.

Some patients were also tested on 2 mg. 6-hourly, with the urine collection being made on the second day. The purpose of using this higher dose is to identify cases due to adrenal tumour in that such patients show an insignificant suppression (Liddle, 1960).

(b) Metapyrone test. This was done as described by Liddle and colleagues (1959). After basal measurement of 17-KGS, Metapyrone (SU-4885, Ciba) was given orally in a dose of 0.5gm. 4-hourly for six doses, commencing at 10 a.m., and 24-hour urinary collections made both during this period, and the next day. These authors found that at least doubling

of urinary 17-OHCS occurred in normal subjects and patients with Cushing's syndrome due to adrenal hyperplasia, but no such rise occurred when due to adrenal tumour.

Tests of carbohydrate metabolism.

Tests were always done after three to five days of preparation on a 300 gram carbohydrate diet.

All the patients had an oral glucose tolerance test (GTT) and many also had a prednisone glycosuria test (PGT) (see Chapter XVIII, page 473 for the test method and normal values).

Three patients had an augmented insulin tolerance test (ITTa) (see Chapter XVIII, page 472 for test method and normal values).

Radiology

Most patients had a pre-operative pre-sacral oxygen insufflation (many done personally) combined with an intravenous pyelogram. Plain x-rays and tomograms of the adrenal areas were then taken.

Radiographs were routinely taken of the pituitary area. All were taken on the Lysholm skull table, in the standard projections (lateral, 25° tilt fronto-occipital, straight antero-posterior).

Method of pituitary implantation

No steroid cover was given to these patients during the operative procedure. All were given the standard sulphadiazine and streptomycin cover for the first 5 days.

The first nine patients were implanted with Au-198 seeds alone, using a dose plan giving 10,000 rads at the diaphragma sellae. The next three patients had a larger central pituitary dose, the plan being to implant both Au-198 and Y-90, each giving 5,000 rads to the diaphragma sellae. In one exceptional case, with carcinoma of the adrenal (case S.Sa.), the pituitary was deliberately ablated; the planned dose at the diaphragma sellae was 300,000 rads.

RESULTS OF PRE-IMPLANT TESTS (Table XVII.I)

To obtain the series of 13 patients with Cushing's syndrome, a considerable number of patients were first screened, having been referred with "suspected Cushing's syndrome". All were initially assessed with a dexamethasone suppression test (4mg./day). In the event, every patient in whom the diagnosis was considered "probable Cushing's syndrome" on clinical grounds had an abnormally high urinary 17-KGS level during the dexamethasone administration. Hence, all came to implantation. There was a single patient in whom the diagnosis of Cushing's syndrome was not considered on clinical grounds to be correct, yet the dexamethasone suppression test was abnormal. She was not treated.

All 13 patients in this series who were treated by pituitary implantation have subsequently had the final diagnosis confirmed by adrenal surgery, the finding of a pituitary tumour (indicating adrenal hyperplasia), a good response to implantation (indicating adrenal hyperplasia), or autopsy. It is therefore possible now to compare the results of the various pre-implant tests with the final diagnosis, in order to assess the diagnostic accuracy of these tests.

Pre-implant basal urinary 17-KGS

There are data from eleven patients with adrenal hyperplasia, one with an adrenal adenoma, and one with adrenal carcinoma. If the basal urinary 17-KGS are inspected in Table XVII.I, there are three patients in whom the mean level was under the upper limit of normal for adults (18 mg.per day). One was a boy of 11 years (case J.Ba.), whose value of 17 mg/day is abnormally high for his age, but the other two (cases E.Ch. and H.Ne.) were middle-aged women without great disability. (Normal values were also found by Horwith and Stokes (1960) in a few of their cases.) These three patients can now be considered further. All three had Cushing's syndrome of marked clinical degree. The two (cases J.Ba. and E.Ch.) who did respond to implantation obtained very striking clinical remissions, thus confirming the diagnosis, and further-

TABLE XVII.I

PRE-IMPLANT TESTS OF ADRENAL FUNCTION.

Patient	Basis for final diagnosis	URINARY 17-KGS (mg./day) **					
		* Basal	* Dexamethasone suppression 4mg/d.	8mg/d.	Metapyrone test Basal	Day of administration	Day after administration
	ADRENAL HYPERPLASIA						
S.Al.	Clear response to implant	25	11	-	-	-	-
J.Ba.	" " " "	17	(19→7)	-	(6	19	22)
M.Ca.	" " " "	45	-	13*	-	-	-
E.Ch.	" " " "	12	11	11_2	12	24	9
R.Da.	Previous subtotal adrx.	64	27_4	-	(29	40	74)
M.Ho.	Autopsy	38	27	-	-	-	-
D.Jo.	Subsequent total adrx.	24	5_2	-	-	-	-
F.Li.	Pituitary tumour radiologically and biopsy	20	19_2	8_2	20	66	122
H.Ne.**	Previous subtotal adrx.	11	-	9*	-	-	-
L.St.	Clear response to implant	32	12	4	35	86	112
F.Ta.	" " " "	51	23	-	51	97	94
	ADRENAL ADENOMA						
B.Ha.	Adenoma excised → remission	23	35	25_2	23	20	20
	ADRENAL CARCINOMA						
S.Sa.	Previous incomplete excision	109	98	-	(200	109	-)

* All figures are the mean of 2 or more values. The duration of tests of less than 5 days is shown as a subscript.

** Bracketed values were obtained after implantation and are quoted if relevant, e.g. incomplete suppression with dexamethasone or definite response to metapyrone. The basal values are shown first in the brackets.

* Collected on 5th and 6th days of fludrocortisol 10mg./day by mouth.

** Steroid measurements made before subtotal adrenalectomy.

more, two had had measurements of cortisol secretion rate by Dr.C.L.Cope (Cope and Black, 1959), and in both this was at least twice the upper limit of normal.

Dexamethasone suppression tests.

Twelve patients had a test with a daily dose of 4mg./24hrs. (or more) and a further patient had only had a test done after operation, but it was still abnormal. It is seen from Table XVII.I that all patients had abnormal results, with excretions above 4mg./24hrs., although in case D.Jo., the elevation was small. In particular, the three patients with basal 17-KGS levels below 18 mg./24hrs. all showed abnormal tests.

Six patients were tested with a dose of 8 mg./24hrs. Liddle's criterion for adrenal tumour was met in three patients (i.e. insignificant suppression); one had an adrenal tumour excised and her disease remitted, but the other two undoubtedly had hyperplasia.

Thus, failure of normal suppression to occur with 4 mg./day appears a sensitive test for the presence of Cushing's disease. Failure of significant suppression to occur with 8 mg./day is consistent with either adrenal tumour or hyperplasia; however, all of eight patients showing some suppression with either regime were proven cases of hyperplasia.

Metapyrone tests.

Five patients in the present series were tested before implantation (Table XVII.I). Four showed a rise in 17-KGS to between double and treble the basal value, while the fifth showed no significant change at all. Two patients tested only after implantation showed similar definite rises. When the final diagnosis of all these patients is inspected, it is seen that all showing rises had adrenal hyperplasia, and the single case with an unchanged level had an adrenal adenoma. This test has therefore been correct distinguishing between hyperplasia and tumour of the adrenals.

Presacral oxygen insufflation radiography

This was carried out in 11 patients before implantation. (An additional patient had already had adrenal surgery (case S.Sa.), and here the side on which there had been incomplete excision of a large mass

of malignant adrenal tissue contained no perirenal gas, while the other adrenal looked a little small). Three showed a definite or suspicious adrenal tumour. In the event, two of these patients had adrenal explorations, and in one the radiologically demonstrated tumour was removed, but in the other, the "tumour" was not present. The third patient with a radiologically "suspected" adrenal tumour did in fact respond impressively to pituitary implantation, and all her steroid tests indicated adrenal hyperplasia. Thus, two false diagnosis of probable adrenal tumour were made radiologically.

There were eight patients in whom a tumour was not shown by x-ray pre-operatively. Both adrenals were demonstrated in all but one. Diffuse enlargement was shown or suspected in one or both adrenals in five.

Tests for diabetes, pre-diabetes, and insulin resistance.

G.T.T.'s were performed in 10 patients. In 4 (with normal fasting blood sugar levels) the G.T.T. was clearly abnormal, and in one, borderline. The series contained two further patients, who had frank clinical diabetes already on treatment (one had retinopathy). Thus, there were 6 out of 12 patients with diabetes mellitus.

A P.G.T. was done in four patients who had a diabetic G.T.T. Only one of these four showed a clearly abnormal PGT with both a raised post-prednisone glycosuria and a raised mid-night blood sugar. A further five patients who had a normal or borderline GTT had a PGT. All these PGTs were normal, with a single marginal exception. It is thus clear that the PGT is very insensitive to the diabetic tendency of Cushing's syndrome.

Three patients whose pre-implant fasting blood sugars were normal were tested by the I.T.T.a. One had abnormal insulin resistance shown, the sum of the 60,90, and 120 minute blood sugars being 160mg.%, and the other two were rather high, being 135 and 144 mg.%. Unfortunately, two of these patients were also obese, so the contribution of their adrenal cortisol excess cannot be gauged. All were re-tested when in good disease remission after pituitary implantation; the two who remained obese showed unchanged insulin resistance, but the non-obese

patient obtained a normal test index of 65mg.%.

Pituitary fossa radiography.

There were two patients in whom abnormalities of the pituitary fossa were shown.

In case D.Jo., there was a normal fossa size and shape in the lateral radiograph, but there was a slight irregularity in the inner surface of the anterior fossa wall. In addition, carotid arteriography done elsewhere had shown a slight upwards and outwards displacement of the right carotid syphon. Now this patient's Cushingoid features had first been noticed at about the time that he began to develop a partial right third nerve paresis. At implantation, a small biopsy was aspirated from the pituitary, and showed cells whose nuclei were abnormally darkly staining and irregular. This was interpreted as being consistent with an invasive pituitary tumour (Fig.XVII.6).

In case F.Li. the pituitary fossa was uniformly enlarged, with an area of 192sq.mm., (normal is <145 sq.mm.- Chapter III) and pituitary biopsy showed an unmistakable mucoid cell adenoma.

Pre-implant calcium measurements

Serum calcium and inorganic phosphate were msasured pre-operatively in 11 patients. These were normal in all cases except case S.Sa. with adrenal carcinoma, where serum calcium was slightly raised to 5.7mEq./l. and inorganic phosphate normal at 1.5mEq./l. This was the only patient among four tested, whc was found to have a raised urine calcium (19mEq./24hr) Serum alkaline phosphatase was normal in all of 12 patients checked.

RESULTS OF PITUITARY IMPLANTATION

During the period between 4/5/59 and 26/6/62, every patient encountered with Cushing's syndrome was initially considered to be caused by adrenal hyperplasia (except case S.Sa. with known adrenal carcinoma); hence, all were treated by pituitary implantation.

Clinical effects of implantation (Table XVII.II).

The effect of the first implant on the Cushingoid facies, hirsutism, blood pressure, and diabetes mellitus, is shown in Table XVII.II. All the patients observed are included in the Table. Post-implant assessments are quoted only if made after six months had elapsed since implantation, and the question of relapse answered only if there had been a remission, and post-operative follow-up had been over a year.

The pre-implant features may first be considered. All thirteen patients looked clinically Cushingoid. Hirsutism, which could only be assessed in females, or males before puberty, was present in eight out of eleven patients. Blood pressure was raised (see footnote to Table) in all but one of the series, and as noted before, six out of twelve patients tested had clinical or chemical diabetes mellitus.

Post-implant clinical assessment of the eleven patients with adrenal hyperplasia

At the post-implant aesessment after six months had elapsed, most of the above features were re-examined. The most striking change was in the Cushingoid appearance. An example of a dramatic loss of this appearance is shown in Fig. XVII.I, along with loss of facial hirsutes. Altogether, loss of the Cushingoid appearance occurred in seven of ten patients assessed.

Hirsutism disappeared in six of seven affected patients, blood pressure fell to normal in four out of eight with raised initial readings, and the oral GTT became normal in three of four patients with an initial diabetic curve.

Peeling of the skin was commonly seen in the second fortnight after implantation in the patients who showed a good general remission. (This was also noted by Aocatruda and colleagues (1960) during the with-

TABLE XVII.II.

EFFECT OF FIRST PITUITARY IMPLANT ON CLINICAL FEATURES, AND DIABETES

	CUSHINGOID FACIES			HIRSUTISM			BLOOD PRESSURE *			DIABETES **		
	Pre	Post	Relapse	Pre	Post	Relapse	Pre	Post	Relapse	Pre	Post	Relapse
					ADRENAL HYPERPLASIA							
S.Al.	++++	–	No	++	–	No	+	–	No	++	–	No
J.Ba.	+++	–	Yes	++	–		++	–	Yes	++	–	
M.Ca.	+++	–	No	+	–	No	+	–			–	
E.Ch.	++	–	No	+	–	No	++	+	No	+	–	
R.Da.	+++						++			++		
M.Ho.	++	++		–	–		++			++	++	
D.Jo.	+++	–	Yes				+	–	Yes	–	–	No
F.Li.	++	++		–	–		+	+		–	–	
H.Ne.	+	+		+	+		++	++		–	–	
L.St.	++	–	No	+	–	No	–	–	No	+		
F.Ta.	++	–	No	+	–	No	++	+	No	+++	+	
No. patients observed	11	10	7	9	9	5	11	9	6	10	9	2
No. patients abnormal	11	3	2	7	1	0	10	4	2	7	1	0
					ADRENAL ADENOMA							
B.Ha.	++	++		–	–		+	+		–	–	
					ADRENAL CARCINOMA							
S.Sa.	++			+			++			+++		

* B.P. ++ = >150/100; + = >120/<80 or <120/>80; – = <120/80

** Frank D.M. = +++
Chemical D.M. = ++
PGT +ve or GTT ? = +
All normal = –

Fig. XVII.I. - Case M.Ca. before and after partial pituitary ablation by Au-198 implantation. The Cushingoid facies and hirsutism were clearly remitting by six weeks.

drawal of steroid therapy.)

A feature that is difficult to quantitate is the psychiatric disturbance that most of these patients present. Relief of the more obvious features such as depression, suspiciousness, and irascability was striking.

Looking at the adrenal hyperplasia group as a whole, there were ten reassessed after six months. Seven of these ten patients were entirely satisfactory, and three (one with a pituitary tumour) showed no response at all. The seven satisfactory patients have now been followed up for one to four years. Two have recently relapsed; one was juvenile (Case J.Ba.), and one was thought to have an invasive pituitary tumour (case D.Jo.).

Post-implant assessment of the two patients with adrenal tumour.

Neither of these two patients showed any clinical response to implantation; neither did implantation have any effect on corticosteroid tests.

Corticosteroid changes after implantation in the hyperplasia cases (Fig. XVII.2)

The serial measurements made after implantation in the eleven patients with adrenal hyperplasia are shown in Fig. XVII.2. The serial plots are of the patients' basal values, and where a dexamethasone suppression test using 4 mg./day was done, the value is indicated with a downwards arrow, and where a Metopyrone test was done, its result is shown by an upwards broken arrow.

Considering first the serial basal values, it is evident that the fall in 17-KGS occurred by the 16th week, and often before this. All those who obtained a good clinical response showed a clear fall in the basal values, irrespective of whether the pre-implant level was normal or not, and the level reached by the 16th week wae maintained unless clinical relapse occurred (2 cases). The two patients who relapsed clinically after an initial good response, both showed a clear rise in the basal 17-KGS output. It thus appears that serial measurements of the urinary 17-KGS after implantation give a good index of disease response.

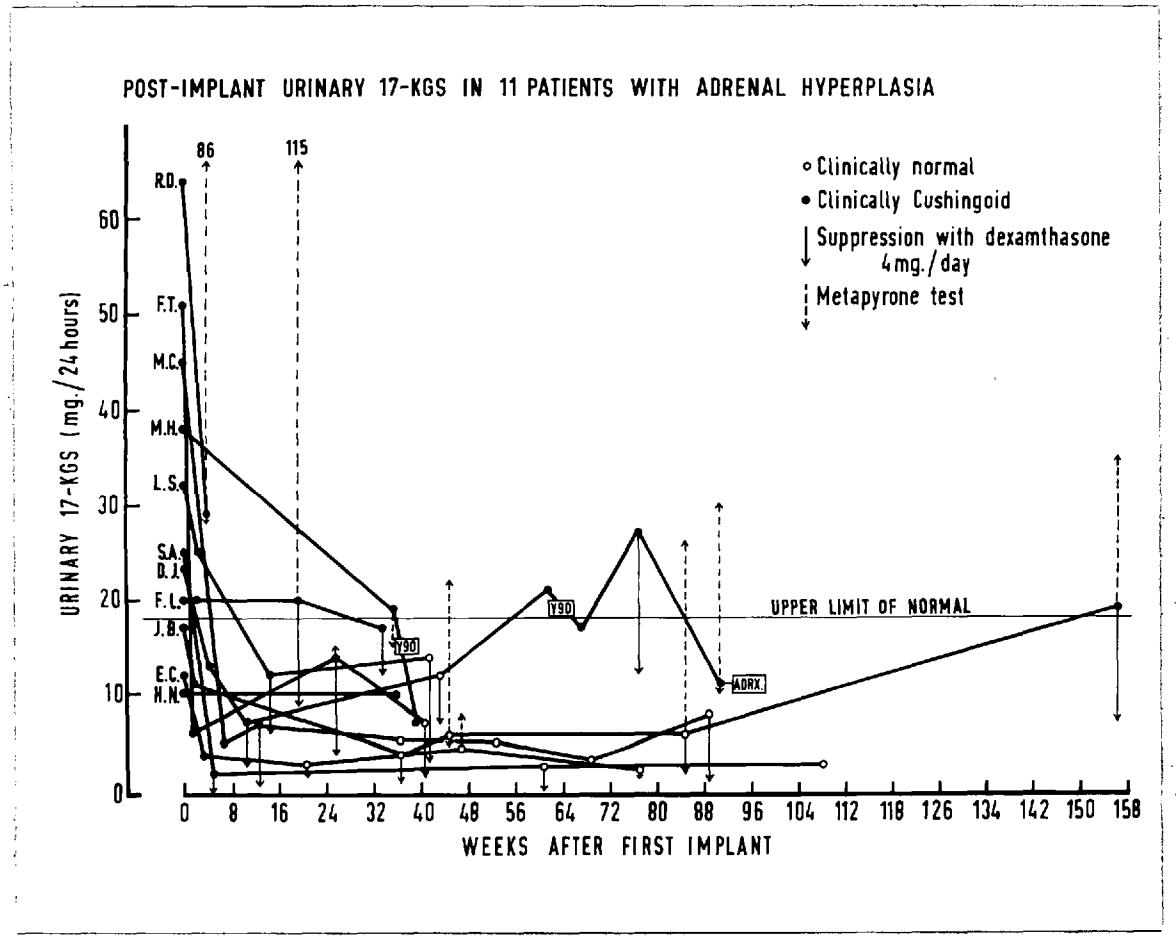

POST-IMPLANT URINARY 17-KGS IN 11 PATIENTS WITH ADRENAL HYPERPLASIA
URINARY 17-KGS (mg./24 hours)
WEEKS AFTER FIRST IMPLANT
86
115
R.D.
F.T.
M.C.
M.H.
L.S.
S.A.
B.J.
F.L.
J.B.
E.C.
H.N.
Y90
Y90
ADRX.
UPPER LIMIT OF NORMAL
Clinically normal
Clinically Cushingoid
Suppression with dexamthasone 4mg./day
Metapyrone test
0
10
20
30
40
50
60
0 8 16 24 32 40 48 56 64 72 80 88 96 104 112 118 126 134 142 150 158

Fig.XVII.2

disease response.

The dexamethasone suppression tests done after implantation can now be examined in the light of clinical disease response. Seven patients were tested during clinical remission and all showed normal basal 17-KGS levels and suppression to under 4 mg./24hrs. Tests were done on four patients who either had failed to show a clinical remission, or were in relapse after an initial response, and none had normal basal levels, and all the dexamethasone test figures were above 7 mg./24hrs.

The two patients with an initial response, and subsequent clinical relapse are specially important in the assessment of the dexamethasone suppression test as a test of activity. Both showed abnormally high basal and suppression values before implantation, normal basal and suppression values during remission, and abnormally high basal and suppression values again when they clinically relapsed. It would thus appear that the dexamethasone suppression test added nothing to the information obtained by the basal 17-KGS in post-implant assessment, and the achievement of normal suppressibility did not preclude subsequent relapse.

Finally, the Metopyrone tests can be evaluated as a means of post-implant assessment. Tests were done on two patients in good clinical remission, and who have not subsequently relapsed; neither showed a significant rise in 17-KGS. A test was done on one patient who had no clinical response, and it showed a rise in 17-KGS from 21 to 115 mg./24hrs. A test done on a patient at the time of initial remission, but who subsequently relapsed, showed a rise from 6 to 22 mg./24hrs. Tests done at the time of relapse in two patients showed clear rises from basal values which were virtually in the normal range. It thus appears that Metopyrone unresponsiveness is a criterion of a lasting remission.

Effect of implantation on two juveniles with Cushing's disease.

Case. J.Ba. was first seen at the age of 11 years, complaining of very severe backache, loss of height, and gross obesity. He looked grossly Cushingoid, there was generalised moderate hirsutism, but no other signs of puberty. The blood pressure was 175/125, and early papilloedema

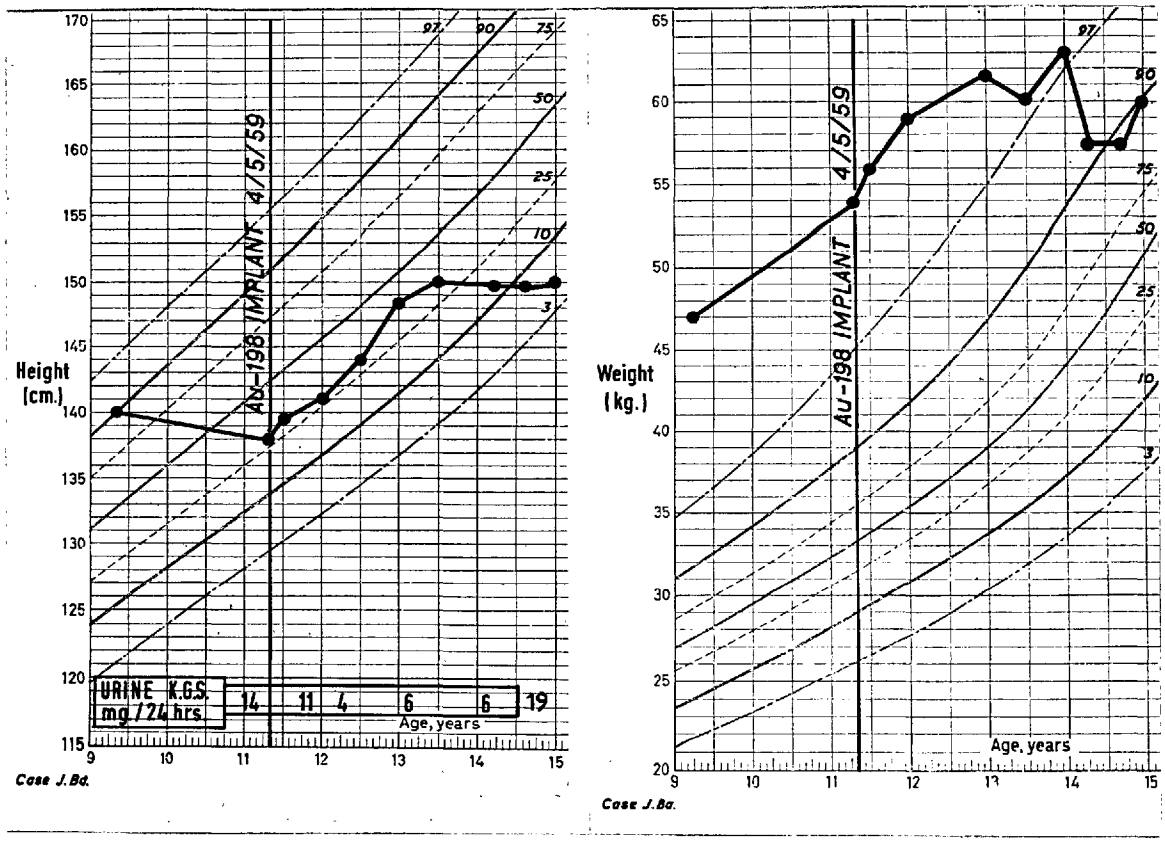


Fig. XVII.3. - Case J.Ba. The height graph shows the effect of the first pituitary implantation in allowing growth to resume. Later, the disease relapsed (17-KGS = 19mg./24hrs.) and caused growth inhibition.

was present. Skeletal x-rays showed gross thinning of the bones, with compression of vertebral bodies.

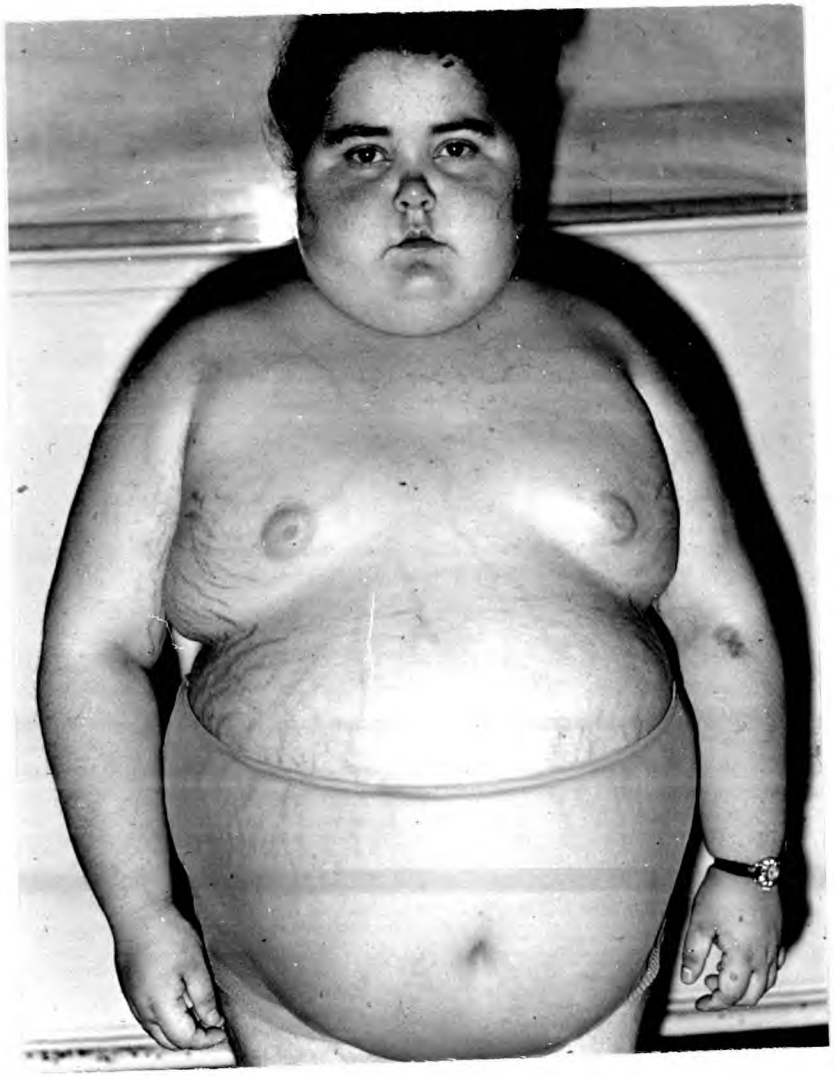
Following implantation he dramatically lost his backache, the hirsutism disappeared, the Cushingoid features almost vanished, and the blood pressure fell to normal with loss of the papilloedema. Skin peeling began three weeks post-operatively, and continued for a few weeks. The GTT became normal. Growth in height was resumed at the normal rate (Fig. XVII.3)., and the serum alkaline phosphatase rose to 60 K.A. units/100ml. by one year, and then fell to normal. The radiological bone density showed a conspicuous increase. Normal puberty occurred at the age of 13 years with testicular enlargement, and full development of secondary sexual features. The urinary F.S.H. was about 12 m.u./24hrs.

Unfortunately he began to relapse at the age of 14, with cessation of growth in height, recurrence of backache, and rise of blood pressure. There was a rise in basal urinary 17-KGS accompanied by brisk responsiveness to Metopyrone. A second implant (not shown in Fig. XVII.2 or XVII.3) with Y-90, aiming to give the diaphragma sellae 10,000 rads was done, just four years after the first operation. Again there was a clinical remission, without causing hypopituitarism, or fall in F.S.H. The urinary 17-KGS fell to 7 mg./day and there was no longer any response to Metopyrone. Normal growth resumed.

Case S.Al. presented with increasing obesity, failure to grow, and exertion dyspnoea. She looked markedly Cushingoid (Fig. XVII.4A) and was moderately hirsute. The blood pressure was 145/95, the GTT was diabetic, and the bones looked thin on x-ray.

At implantation, a small pituitary biopsy was obtained. Anterior pituitary architecture was normal, and a few Crooke cells were present.

Following the implantation of two Au-198 seeds into each side of the pituitary gland, the Cushingoid features became less marked in a week, and entirely regressed as is evident in the photograph in Fig.XVII.4B taken seven months post-operatively. There was a period of a few weeks when the skin peeled. The hirsutism was soon lost, blood pressure fell to normal, and the GTT became normal. Growth in height resumed at the



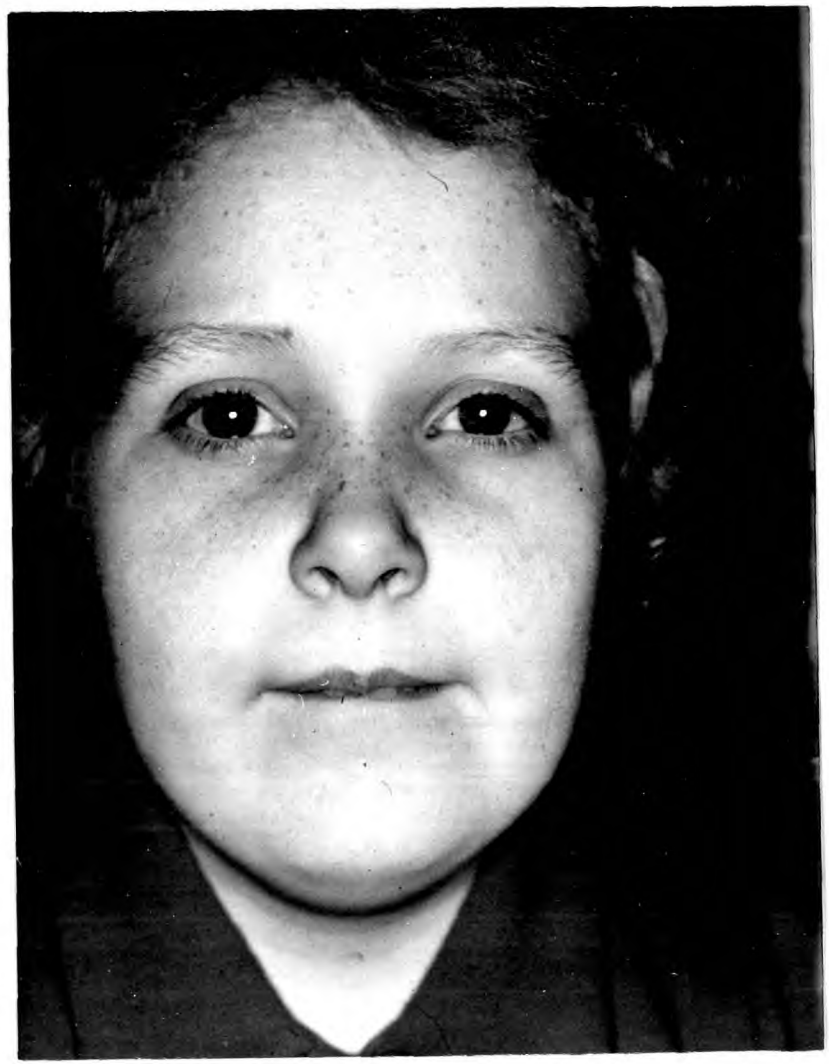


Fig. XVII.4 - Case S. Al. (a) Before implantation. (b) 7 months after implantation.

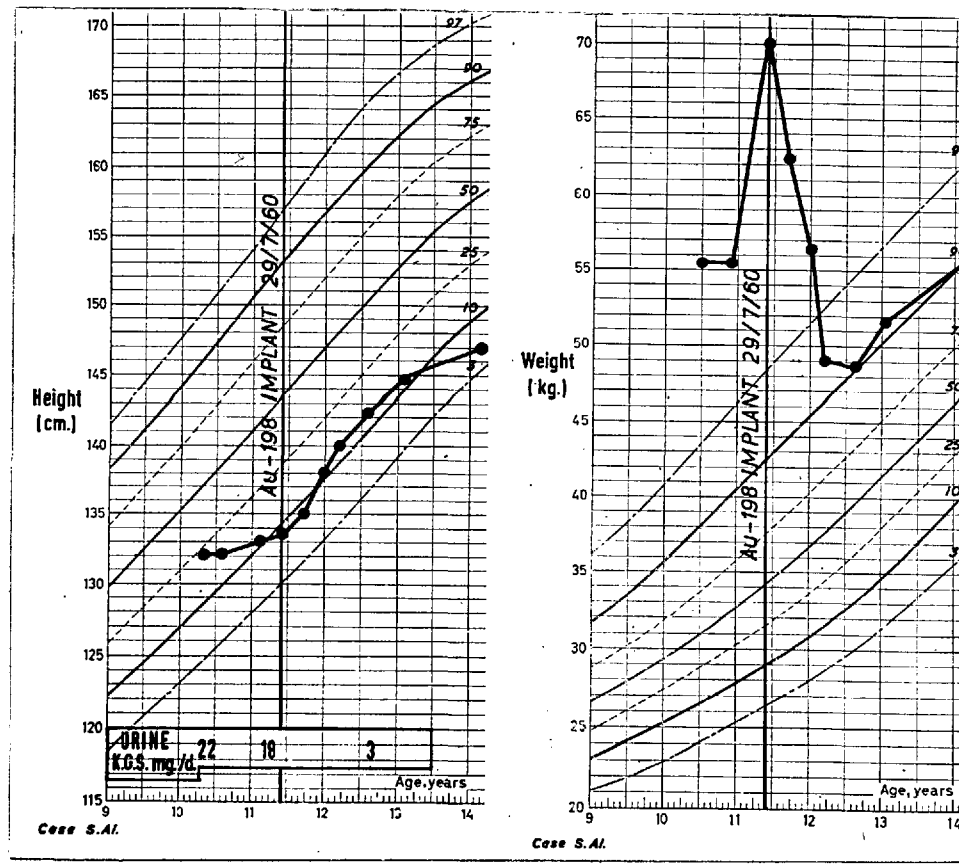


Fig. XVII.5 - Case S.Al. The graphs show the effect of pituitary implantation on growth.

normal rate, as in Fig. XVII.5. The bones became radiologically denser, and the serum alkaline phosphatase rose from 15 K.A. units to a peak of 24 K.A. units/100ml., nine months post-operatively.

It was of interest that she was steroid dependent for the first few months after operation: slow steroid withdrawal was attempted six weeks post-operatively, but the development of a severe cortico-steroid-deficiency syndrome necessitated the re-introduction of cortisone after seven days. During steroid withdrawal, the urinary 17-KGS level was 4 mg./24hrs. After steroids had been finally withdrawn nine months post-operatively, basal urinary 17-KGS were consistently about 4 mg./24hrs. She had shown no sign of puberty by the age of 14, 3 years post-implant, and the urinary F.S.H. had not risen, being under 8 m.u./24hrs. The growth in height began to lessen at this stage, and raises the question of slight hypopituitarism. However, her bone-age was slightly advanced and her energy and well-being are perfectly normal. There was no hint of recurrence of Cushingoid appearance nor a rise in basal urinary 17-KGS. Her mother was short and had a late menarche, so the final assessment must await further follow-up.

General endocrine effects of partial pituitary ablation for the treatment of Cushing's syndrome.

There was no instance of clinical myxoedema. Clinical steroid dependency was only incurred in one instance (case S.Al.) and this was but temporary.

Post-implant I-131 uptake measurements made in five cases showed normal values in four, and rather a low uptake of 19% in the fifth; this last patient showed no rise in cholesterol nor clinical evidence of myx-oedema in a follow-up of 18 months, and menstruation still occurred.

Six of the women treated were premenopausal. Two who had amenorrhoea resumed menstruation after implantation, and three who were having periods continued to do so without change after implantation. However, in one aged 25 years, hitherto regular periods gradually became scantier and infrequent after operation, and finally ceased; the urinary FSH level was normal and she developed hot flushes; there was no other suggestion of hypopituitarism.

Re-implantation

A second implant was done in four patients of the present series.

Case J.Ba. initially had an implant of two Au-198 seeds which were rather poorly placed, so an additional Y-90 seed was inserted soon after. After an initial good clinical remission, the disease reappeared, and a third implant was done four years after the first. This was done with Y-90 alone, the planned dose to the diaphragma sellae being 10,000 rads. A striking clinical and biochemical response was again obtained.

Case M.Ho. had a second implant eight months after the first, because there had been no clinical or biochemical improvement. The second implant was done with a larger dose of Y-90, planned to give the diaphragma sellae 300,000 rads, and produce total pituitary destruction. The reason for doing a total ablation rather than a partial, was the desperate clinical condition of the patient. Unfortunately, she died three months later of an (unrelated) subarachnoid haemorrhage, and the clinical response to the second implant was not assessed. However, the basal urinary 17-KGS level had fallen to 7 mg./24hrs. 3 weeks after operation, and at autopsy, the pituitary was found to be totally destroyed.

Case R. Da. showed no clinical response a month after the initial implant, and urinary steroid levels were still abnormally high with marked Metopyrone responsiveness, so re-implantation with Y-90 was done, the planned dose to the diaphragma sellae being 10,000 rads. He subsequently obtained a striking clinical remission.

Case D.Jo. was thought to have an invasive pituitary tumour which had not expanded the pituitary fossa. There was an excellent clinical and biochemical remission after an initial implant with Au-198 alone, with a planned dose to the diaphragma sellae of 10,000 rads. Pituitary biopsy (Fig. XVII.6.) suggested an invasive type of tumour. Relapse occurred after 16 months. The patient had very extensive drug-resistant pulmonary tuberculosis, so there was considerable urgency in securing a speedy remission. Adrenalectomy was considered, but was precluded by the chest condition. Hence a second pituitary implant was done, using Y-90 alone, planned to cause total ablation, the dose at the diaphragma

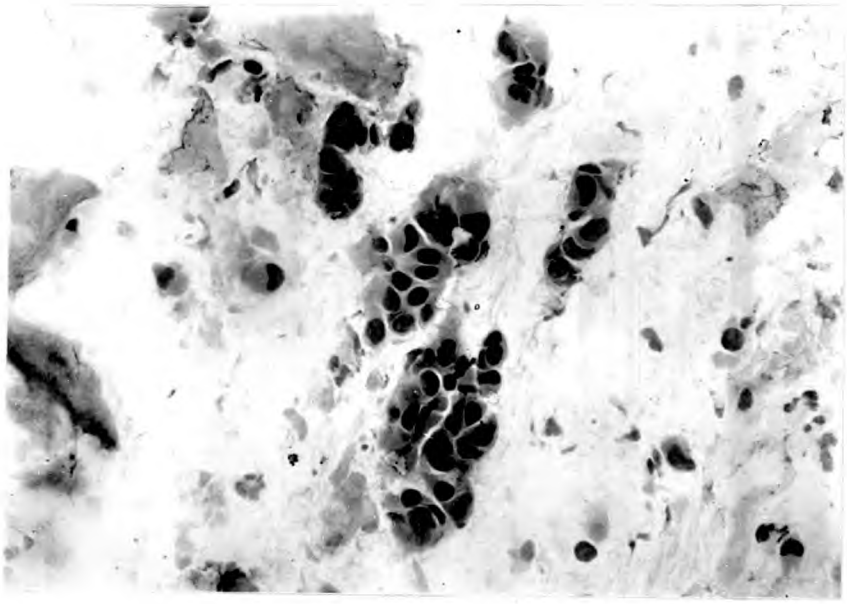


Fig. XVII.6 - Pituitary biopsy in case D.Jo. The nuclei are darkly-staining and rather irregular, suggesting an invasive tumour. (H and E.X370).

sellae being 300,000 rads. No improvement in Cushing's disease resulted, yet the I-131 uptake fell to 13%, and the patient probably became myxoedematous. Adrenaleotomy was then unavoidable; bilateral adrenal hyperplasia was found. The operation was followed by serious post-operative complications, but recovery occurred, and the Cushing's disease remitted.

Complications of pituitary implantation for Cushing's syndrome.

Complications were very few. There was a total of 17 implants done in thirteen patients.

Among the thirteen first implants, there were two complioations. Case D.Jo., whose disease had begun with a partial right third cranial nerve lesion, had an immediate increase in paresis of this nerve, but this later greatly improved and became virtually normal. At the time that this aggravation occurred, there was a total right ophthalmoplegia lasting a few days, along with a right inferior nasal field defect and analgesia in the territory of the ophthalmic division of the right fifth nerve. It is considered that these temporary neurological defects were a consequence of oedema in a pituitary tumour. During the implantation procedure in case R. Da., C.S.F. emerged from a properly placed implant needle. This continued to leak, and could not be arrested by the insertion of a screw five weeks later, owing to the softness of the fossa wall. It was corrected by the insertion of a muscle graft (Mr. G.H.Bateman) by a direct nasal operation.

Re-implantation was done in four cases. The only complication was again with case D.Jo., where a total ablation was attempted by implantation of Y-90 with a planned dose to the diaphragma sellae of 300,000 rads. Nineteen months post-operatively, a C.S.F. rhinorrhoea developed, and could not be arrested by the insertion of a screw, so the patient was referred for neurosurgical repair (Mr. M.A.Falconer); a hole was found in both the anterior and posterior walls of the sella and both were successfully plugged by muscle. No tumour or pituitary tissue was seen.

There were no instances of permanent diabetes insipidus, although temporary pitressin administration was required in two patients.

DISCUSSION

From the data reported here, there is no doubt that some patients with Cushing's syndrome due to bilateral adrenal hyperplasia can be effectively treated by partial pituitary ablation done by needle implantation. It appears that all signs of the disease may remit, and that clinical improvement may be anticipated as early as a week after operation, or not until 6 months. The irradiation dose which was used in the first instance for patients suspected of having bilateral adrenal hyperplasia is about one thirtieth of the dose required to totally ablate the pituitary. It is not therefore surprising that hypopituitarism did not occur in any patients treated with this dose.

Implant dose plan

It might be questioned whether the dose chosen for use in the first instance was adequate, because satisfactory clinical remissions were only obtained in 7 of 10 patients with hyperplasia who were followed up for six months, and remission was but temporary in two cases. Second implants of Y-90 alone of only about 10,000 rads dose at the diaphragma sellae were effective without causing hypopituitarism in the two cases so treated, so it would appear that a dose at the diaphragma sellae of about 20,000 rads may be appropriate for the initial implant. The other factor to be considered in recommending an initial dose is the type of irradiation source to be used. The patients in the present series were all treated in the first instance with either Au-198 alone giving a dose of 10,000 rads at the diaphragma sellae, or combined Au-198 and Y-90 each giving about 5,000 rads to the diaphragma sellae. A disadvantage of combining the two different types of source is the difficulty in placing the several seeds in ideal position. It is much easier technically to implant but one source on either side of the gland. The reason for using Au-198 at all was to avoid hypopituitarism, yet to give the entire gland fairly heavy irradiation, but now that it is evident that hypopituitarism has not resulted from Y-90 in doses of 5,000 to 10,000 rads at the diaphragma sellae, even if preceeded by

or combined with supplementary irradiation by Au-198, the need for using Au-198 at all seems obviated. It is thus argued that, in the absence of requirement for further growth or fertility, it would be ideal to use Y-90 alone, aiming to give the diaphragma sellae 20,000 rads. Where these two desiderata are important, it would perhaps be wise to continue with the original plan of implanting Au-198 alone, and planning the dose at the diaphragma sellae to be 10,000 rads, at least in the first instance. In the patients with pituitary tumours where the risk of local extension is serious, and response to implantation poor, a much higher initial dose would be justified; perhaps a dose of 50,000 rads at the diaphragma sellae would be suitable.

It is important to consider the possible existence of rare patients with adrenal hyperplasia whose disease cannot be relieved by pituitary destruction. Case D.Jo. seems quite a likely example, in that at craniotomy, no anterior pituitary tissue was found, yet the Cushing's disease was very active; adrenal hyperplasia was subsequently found at adrenalectomy.

This raises the question of management of the patient who does not respond to a first implant, yet in whom the diagnosis of adrenal hyperplasia had been made. It would be reasonable to offer a second implant, but in the event of failure of response by three months, to proceed to adrenalectomy. The ideal type of implant for a second operation cannot yet be gained from the present study. A suitable interim plan would be to use a near-ablation dose of Y-90 (such as 50,000 rads at the diaphragma sellae) in those in whom growth and fertility are not crucial, but only 10,000 rads where these are important.

Complications from implantation

Complications in this series were few, and confined to two patients. The first (case D.Jo.) probably had an invasive pituitary tumour, which appeared to have been totally destroyed by the two implant procedures. He sustained temporary cranial nerve palsies immediately after the first operation, and C.S.F. leakage after the second. The second case (R.Da.) was unfortunate in having a sunken pituitary. This is a rare anatomical anomaly which cannot usually be anticipated pre-

operatively, and must be regarded as an inevitable hazard of all types of implantation. But in the case of patients with Cushing's disease, it is especially hazardous, in that the bone of the sellar wall is very soft, and does not tightly grip a screw. In both cases, the leakage was arrested surgically. It may be emphasised that case R.Da. could not have been treated in any other way, as total bilateral adrenaleotomy had been attempted but a remnant must have been left behind, and further exploration was deemed impossible.

Distinction between adrenal tumour and hyperplasia

It seems that if the correct dose of interstitial irradiation is given, most patients with Cushing's disease will obtain a good remission. However, the total failure of implantation to alter the disease in the patients with an adrenal adenoma and adrenal carcinoma underlines the critical importance of making this distinction correctly in the preliminary assessment. The means of making this distinction can now be reviewed from the present series. Pre-sacral oxygen insufflation coupled with an intravenous pyelogram was not reliable. The single case of adrenal adenoma was correctly shown, but appearanoes suggestive of tumour were found in two other cases who in fact responded well to implantation or had a negative exploration. Two similar false positive diagnoses of adrenal tumour were made in Iannocoone's series (1960). Further, it is inevitable that false negative diagnoses of adrenal tumour would be made with this technique where the tumour is very small. Adrenal hyperplasia cannot be diagnosed with confidenoe from the slight enlargement of the adrenals often present in these cases. Thus adrenal radiology is not very helpful; probably its value is in the occasional case where a tumour can be unequivocally shown.

The distinction between tumour and hyperplasia was shown by Liddle (1960) to be made by finding that in the tumour cases the urinary 17-OHCS could not be suppressed at all by dexamethasone 8mg./day. He found that all of 27 patients with adrenal hyperplasia obtained a reduction in 17-OHCS of at least 50% with this dose (or less), while none of 7 patients with adrenal adenoma or carcinoma showed any significant

change. Case B.Ha. of the present series who ultimately had her disease cured by the excision of an adrenal adenoma, showed complete lack of suppression on this large dose of dexamethasone. However, case E.Ch. of the present series also showed no suppression; she obtained an excellent response to pituitary implantation, making the presence of a functioning adrenal adenoma highly unlikely. There has recently been a further case with a pituitary tumour and hyperplasia, with autopsy proof. Similar lack of suppression in a few patients with proven hyperplasia has been reported (e.g.Sprague et al., 1961 and Silverman et al., 1963). Thus, it would appear that failure of suppression in this test can only be regarded as consistent with an adrenal tumour, and not diagnostic. The occurrence of distinct suppression appears to exclude tumour.

The Metopyrone test was introduced by Liddle and his colleagues in 1959, and appeared to distinguish patients with adrenal hyperplasia from those with adrenal tumour without fault. They found that all of seven patients with adrenal hyperplasia showed a rise in urinary 17-OHCS to between double and treble the basal value, whereas none of four patients with biochemically suspected (lack of dexamethasone suppression) or histologically proven adrenal tumours showed more than a trivial rise. In the present series, all of six patients showing a rise to between double and treble the basal value had adrenal hyperplasia, and the two patients who showed no rise had an adrenal adenoma or carcinoma. This test therefore appears reliable.

It was of considerable interest to find that the patient with a mucoid cell pituitary tumour showed a clear suppression with dexamethasone, and rise with Metopyrone. She showed no response to implantation. The question of malignant disease of non-endocrine tissue as the stimulus for Cushing's syndrome must be remembered, the likely basis for this being the secretion of an ACTH-like material by the tumour. Dexamethasone in a dose of 8 mg. daily does not suppress the urinary corticosteroids, (Hudson and Evans, 1962, Meador et al.,1962) thus resembling adrenal tumour. Two cases were encountered during the present study and both rapidly succumbed. Dexamethasone and Metopyrone caused no change in corticosteroid levels. Fortunately, these cases

can be suspected when the serum potassium is abnormally low (<3.0mEq./l) (Bagshawe, 1960), although malignant disease is not invariably present when hypokalemia is found.

Effect of implantation on P.G.T.

Now that actual steroid measurements can be made, there is little diagnostic value in the ancillary tests of carbohydrate metabolism. Improvement in abnormality after therapy is of course most useful in following progress. It was of interest to find that there was usually no significant abnormality revealed in either the mid-night blood sugar or the overnight glycosuria following the administration of prednisone in the prednisone glycosuria test. In particular, this was so for three of the four patients who had chemical diabetes shown by an abnormal G.T.T. ' In contrast, abnormal values had been found in all the fourteen patients tested with this test who had an abnormal G.T.T. but did not have Cushing's syndrome. Possibly the patients with Cushing's syndrome possess such a high endogenous circulating steroid level that the addition of the prednisone has an unusually small effect.

Comparison with adrenal surgery

The results of the present series can now be compared with series treated in a more conventional way, by adrenal surgery. Two types of adrenal operative approach have been used; these are subtotal adrenalectomy and total adrenalectomy. The advantage of subtotal adrenalectomy is the chance of avoiding steroid dependency, but the disadvantage is a risk of disease recurrence. The less extensive the resection, and the younger the patient, and the more acute the disease, the more likely is recurrence (Mason et al., 1958). A large series of 75 subtotal adrenalectomies for adrenal hyperplasia from the Mayo Clinic has been followed up by Sprague and colleagues (1961). They reported that about a third of the patients have had disease recurrence and this number will no doubt increase with longer follow-up. On the other hand, only a "small minority" remained satisfactory yet did not require cortisone. A smaller recurrence rate was reported in a Belfast series by Montgomery and Welbourn (1963). There was only one recurrence among 20 patients, but about half the patients required

steroids. The evidence for and against subtotal adrenalectomy has been extensively reviewed by Sprague and colleagues, who appear to slightly favour total excision, especially in the younger and more acute cases. Thus, when the results of the initial implantation using the very low dosage used here are compared with surgery, the complete absence of steroid dependency is a considerable advantage of implantation, but the frequency of immediate disease remission was less than with radical subtotal or total adrenalectomy, and recurrence of disease probably comparable with subtotal adrenalectomy.

When surgical mortality and morbidity are reviewed, it appears from three series totalling 192 operations that the surgical mortality is usually about 10% (Mason et al., 1958; Sprague et al., 1961; and Montgomery and Welbourn, 1963). In addition, there was significant morbidity. On the other hand, there were no deaths in 35 adrenal operations in the series of Horwith and Stokes (1960). Thus, the lack of mortality from implantation is a very definite advantage. Morbidity although of a different nature in the two operations, may be less with implantation.

Because of the risk of recurrence following subtotal adrenalectomy, Soffer and colleagues (1956) tried a combination of intensive pituitary irradiation with unilateral adrenalectomy, and found that half their patients obtained satisfactory results. Hence unilateral adrenalectomy after "failed implantation" may be worthy of trial.

The problem of rapidly growing pituitary tumours in some patients with Cushing's disease is causing further appraisal of adrenalectomy in the treatment of adrenal hyperplasia. This has been reviewed by Sprague and colleagues (1961), who found fourteen cases; ten were present before adrenalectomy, and four appeared subsequently. They felt that it was likely that tumours were present before adrenalectomy, but that they grow faster after removal of the adrenals. They are predominantly chromophobe. Curiously, melanosis has been present in most reported cases, and it seems likely that at least some of these tumours produce corticotrophin and possess melanocyte stimulating

properties. Unfortunately, some of these tumours become malignant (Hangen et al., 1960). In the present series, there was one instance of a pituitary tumour shown radiologically by the sellar area in the lateral skull radiograph being 192 sq.mm. (as measured on the film), the extreme upper limit of normal being 145 sq.mm. (Chapter III). Among the eight patients with Cushing's syndrome who presented after the termination of the present series, there were three further cases. Thus, out of 21 patients with Cushing's syndrome, irrespective of final diagnosis of etiological type, there were four with moderately enlarged sellae. Significantly, none responded satisfactorily to implantation, and will be treated by a higher dose in the future.

Results of pituitary irradiation and neurosurgery.

External pituitary irradiation has been used as the primary treatment of Cushing's disease. Dohan et al.(1957) and Soffer et al.(1961) gave doses of 4,000 to 5,000 rads. From their own series of 12 and 14, and a review of the literature, they showed a remission rate of about 50%. Direct neurosurgical attack on the pituitary has also been tried with success (Luft et al., 1957, Ray, 1960), especially when complicated by a pituitary tumour.

Treatment of Cushing's disease by means of interstitial irradiation has occasionally been reported. Beneficial results were obtained by radon seeds inserted at craniotomy by Pattison and Swan (1938) and by Northfield, (1949). More recently needle implantation was reported by Molinatti and his colleagues (1960). The latter, using a single pellet of Y-90, of activity 5.4mC obtained a very satisfactory remission in one case, without causing hypopituitarism, but a second implant was needed in the second patient. As the shape and thickness of their pellets are approximately the same as used in the present study, the peak dose at the diaphragma sellae in an average sized fossa would be about a million rads, while the dose to the gland edge would be about 200,000 rads. Thus, one would expect this dose to cause necrosis of the diaphragma sellae, and run the risk of total pituitary

ablation, in a gland of average dimensions.

Test criteria for satisfactory pituitary implantation.

It appears that the achievement of a normal basal value for urinary 17-KGS is but a minimal criterion, because two patients of the present series had values in the normal range pre-operatively (although incompletely suppressed by dexamethasone 4mg./day). The achievement of normal suppressibility by dexamethasone 4 mg./day occurred in the seven clinically satisfactory patients, but two such patients subsequently relapsed. The lack of relevance of dexamethasone suppression values after external irradiation was also found by others. Liddle (1960) did suppression tests using 2 mg./day in 6 patients with a good clinical response to external irradiation. Three still showed poor suppression yet normal basal values. Futterweit and his colleagues (1962) found that two of four patients in complete clinical remission after pituitary irradiation showed insuppressible urinary 17-OHCS with dexamethasone 2 mg./day, yet normal basal levels.

When the post-irradiation Metopyrone tests of the present series were inspected, the two patients tested when in remission and who did not subsequently relapse showed no response to Metopyrone. One patient tested during a temporary remission showed a brisk response, and two patients in relapse were also responsive. From this small number of patients tested, it would appear that Metopyrone unresponsiveness is a desirable objective. Liddle and colleagues (1959) found that all of four patients in remission from Cushing's disease following pituitary irradiation exhibited virtually no reponse. In contrast, Futterweit and colleagues (1962) found that all four of their series who obtained a remission after pituitary irradiation (with or without unilateral adrenalectomy), still showed a distinct Metopyrone response. Only a prolonged follow-up of all these series will show whether it is necessary to administer a pituitary irradiation dose such that Metopyrone unresponsiveness is achieved.

Management where growth and fertility are important.

Two special types of patient merit special consideration - juveniles, and those in whom fertility is important. No patient in the present series has provided an opportunity for fertility to be tested after implantation although menstruation has occurred and normal urinary gonadotrophin levels have been found. The question of growth in the juveniles can also be partly answered. It was clear that both juveniles resumed growth in height at the normal rate soon after implantation and one developed normal pubertal changes. However, both stopped growing after about two years. In one (J.Ba.) this was due to disease recurrence, and growth resumed after a second implant. In the other (S.Al.) the cause of growth cessation is less clear, and hypopituitarism may be suspected because there has also been no pubertal development. However, further follow-up is needed to confirm this supposition.

It therefore remains sub judice whether patients with growth and fertility requirements are best treated by pituitary implantation or adrenalectomy. As some of the results in these patients have been quite encouraging, it would seem reasonable to continue to treat such patients in this manner, on the dose plan already discussed.

SUMMARY

1. Thirteen patients with clinically obvious Cushing's syndrome have been studied before and after pituitary implantation. The exact etiology was established in all patients by positive response to pituitary implantation, surgical examination of the adrenals, the radiological demonstration of a pituitary tumour with biopsy support, or autopsy.

2. The presence of adrenal hypersecretion of cortisol was shown by abnormally high levels of urinary 17-KGS in only ten out of the thirteen patients. However, failure of dexamethasone (4mg./24hrs.) to suppress this in the normal manner to under 4 mg./24hrs. was found in all of eleven cases tested.

3. The dexamethasone suppression test was assessed as a means of distinguishing patients with adrenal tumour from those with hyperplasia. Where insignificant suppression resulted from 4mg./24hrs., 8mg./24hrs. was administered. Twelve patients were tested. Nine showed a significant suppression of urinary 17-KGS, and three did not. All nine showing significant suppression were independently shown to be cases with adrenal hyperplasia. Of the three showing no suppression, two had adrenal hyperplasia, and one an adrenal adenoma. Failure of suppression to occur with this test is consistent with both adrenal tumour and hyperplasia.

4. The Metapyrone test was also assessed as a means of distinguishing cases of adrenal tumour from those with hyperplasia. Seven patients were tested. Six showed a rise in urinary 17-KGS, and all were independently shown to have adrenal hyperplasia. Two did not show a significant rise, and were cases of adrenal tumours.

5. Presacral oxygen insufflation radiography was done in eleven patients. A definite adrenal tumour was diagnosed with certainty in one case and surgically proven correct. A probable adrenal tumour was shown in two further cases, and was disproved in both.

6. It was shown that out of 21 consecutive patients with Cushing's syndrome, irrespective of etiological type , four had pituitary tumours shown by plain radiographs, and confirmed by pituitary biopsy.

7. Pituitary implantation was done in eleven patients whose final diagnosis was adrenal hyperplasia. Of ten patients followed up for at least 6 months, seven obtained a clinical remission and normal basal urinary 17-KGS. Two patients later relapsed; one responded to a further partial pituitary ablation, and the other (invasive pituitary tumour) failed to respond to total pituitary ablation.

8. Partial pituitary ablation had no effect in the single patient with adrenal adenoma, and total pituitary ablation no benefit on the patient with adrenal carcinoma.

9. The implant plan for partial pituitary ablation was to give a dose at the diaphragma sellae or 10,000 rads from centrally placed seeds of Au-198 alone, or from a mixed implant of Au-198 and Y-90. No such implant produced hypopituitarism to the point of requiring permanent replacement therapy.

10. Objective criteria indicative of a satisfactory and permanent remission were normal basal urinary 17-KGS and Metapyrone unresponsiveness.

11. Complications arising from the thirteen initial implants, twelve of which were planned for partial ablation, and one for total ablation, were a single instance of C.S.F. leakage and a temporary exacerbation of cranial nerve lesions in a patient thought to have an invasive pituitary tumour.

    Four re-implantations were done, two being partial ablations, and two total. The only complication was one instance of C.S.F. leakage (invasive pituitary tumour).

CHAPTER XVIII

THE EFFECT OF PITUITARY IMPLANTATION ON ACROMEGALY

The objective in the treatment of acromegaly is suppression of pituitary hyperfunction and prevention of further tumour growth, yet if possible without the production of hypopituitarism. Unfortunately, the prognosis of acromegaly is still largely a matter of opinion, so that until an untreated series is reported upon in detail, with observations continued to death, it is impossible to make a complete evaluation of the effect of any particular therapy. Bishop and Briggs (1958) have however reported that 48% of their series of about 100 acromegalios died before the age of 50, and 80% had died by the age of 60; most deaths were from cardiovascular causes.

In the meantime, assessment of the efficacy of any particular treatment can be based only upon change induced in the patient, rather than upon extension of survival and protection from the complications of the disease. There is an impressive list of hazards which the untreated acromegalic runs. It is therefore by contrasting the hazards of treatment with the extent of disease regression, that alternative treatments can be compared. Good objective indices of acromegaly activity have only just become available; direct assay of serum human growth hormone should be most useful (e.g. the methods of Hunter and Greenwood (1962) and Glick et al., 1963).

Pituitary implantation was undertaken for acromegaly against a background of contrasting alternative treatments which will be reviewed in the discussion. On the one hand, conventional external irradiation has undoubtedly led to some regressions, but is often without effect; yet it is relatively safe if dosage is kept below well-established maxima. More recently, larger doses have been given safely by high-energy heavy particle irradiation. On the other hand, there is neurosurgery, carrying an inevitable risk of operative mortality, and morbidity, yet often leading to disease regression and in particular, relief of chiasmal compression. However, there has been a definite tumour recurrence rate, which can be diminished if supplementary radiotherapy is

given.

Because neither external irradiation or neurosurgery were entirely satisfactory, Northfield (1949) first attempted pituitary implantation with radon at craniotomy, and later Bauer and Klar (1950) tried percutaneous application of electro-coagulation. The present study is an extension of these early efforts.

At the beginning, there was little information upon which to base the irradiation dose-plan, apart from the results of external irradiation. An additional problem was the lack of a method of defining the position of the lateral and superior surfaces of the tumour. As the objective was to irradiate heavily the entire tumour, without inevitably inducing hypopituitarism, it was initially considered best to use a source with a gamma emission. This would have the advantage of giving a reasonable dose at the tumour surfaces, without causing extensive central necrosis. Gold-198 was selected, and the dose at the tumour periphery was planned to be 10,000 rads. In particular, the dose at the estimated "normal" level of the diaphragma sellae was planned at 10,000 rads. This limit was imposed by the knowledge that a cumulative dose much above this, given by external irradiation, would very likely damage the chiasma (reviewed in Chapter IV) A margin of safety was present, in that in many cases the superior surface of the tumour would be above the "normal" radiological level of the diaphragma sellae. Because of the penetrating nature of the emission of Au-198, at least some irradiation would be given to unknown extensions of tumour. In the event, it was found that although irradiation damage to the chiasma did not occur with this dose plan, only a minority of patients obtained sufficient clinical regressions of their disease, and re-implantation was often necessary. Therefore, this initial dose plan was modified to give a deliberate necrotic dose to the tumour centre, by inserting both Y-90 and Au-198 sources, keeping the total dose at the diaphragma sellae at 10,000 rads, so that the risk to the chiasma would be unchanged, or even diminished.

The purpose in this chapter is to describe the results of treatment of acromegaly by pituitary implantation. It was an additional objective

to evaluate certain proposed tests as indices of activity by comparing results before and after implantation, especially in patients having an obvious regression in acromegalic facies.

PATIENTS TREATED AND RESULTS FROM PREVIOUS EXTERNAL IRRADIATION

A total of 22 patients had implant operations for acromegaly up to 7/9/62, and the results of all will be considered in this chapter. Their ages were 30 to 62 years; 9 were males. The first operation was done on 29/8/58. Actually, only 20 patients had the operation satisfactorily completed, because an enormous intra-pituitary cyst precluded the insertion of any radioactive material in one patient, and in a second patient, a cyst was discovered after the ejection of the first seed on either side, and hence no further seeds were implanted. The longest duration of the post-operative follow-up was 48 months. Most patients were seen 3-monthly at the out-patients clinic, and were admitted for more detailed testing at 3, 6 and 12 months.

All the implanted patients were judged on clinical grounds to have active disease. In none had there been regression of the acromegalic facies or significant loss of symptoms, either spontaneously or as a result of previous external irradiation. By coincidence, there were no patients with a visual field defect.

The results from previous external irradiation are detailed in Table XVIII.I for the 8 patients treated in this way. In about half, this treatment had been given at Hammersmith Hospital and the patients assessed by the writer before and after. In the remainder, the information was obtained from the referring hospital. It is seen that none of these patients obtained regression of the acromegalic facies, and there was little significant improvement in symptoms. The augmented insulin tolerance test (ITTa - see later) was abnormal after therapy in all of 6 patients tested, and the diabetes mellitus of one patient remained unimproved.

TABLE XVIII.I.

RESPONSE OF ACROMEGALY TO PITUITARY IRRADIATION (8 PATIENTS)

PATIENT	Date of DXR	Total Dose (rads)	Weeks of DXR course	Headache			Paraesthesiae			Hand vol. fell by 50 ml.	Augmented Insulin tol. test after DXR	Facies regressed
				Present before DXR	Temporary improvement	Permanent improvement	Present before DXR	Temporary improvement	Permanent improvement			
C.St.(a)	1953	3,900	6	+	-	-	+	-	-	-	0	-
(b)	1955	3,000	4	+	-	-	+	-	-	-	168	-
J.Fi.	1959	4,000	3	+	+	+	-	0	0	-	148	-
S.Cl.	1957	4,000	3	-	0	0	+	+	-	-	179	-
F.Ez.	1959	1,750	3	+	+	+	-	0	0	0	227	-
M.Wo.(a)	1955	1,020	1	+	0	-	+	0	-	0	0	-
(b)	1956	1,020	2	+	-	-	+	0	-	0	0	-
(c)	1958	2,000	3	+	-	-	+	-	-	0	147	-
M.Fo.(a)	1955	3,040	4	+	+	-	+	-	-	-	0	-
(b)	1956	3,000	5	+	+	-	+	-	-	-	0	-
K.Ro.	1957	4,000	3	+	-	-	+	+	-	-	183	-
S.Ri.	1959	3,500	4	+	-	-	-	0	0	0	D.M.	-
Totals:		1750 to 6,900 rads cumulative dose		7/8	3/7	2/7	5/8	2/5	0/5		6/6 abnormal	0/8

Symbols: + = yes
- = no
0 = unknown or irrelevant.

METHODS OF ASSESSMENT OF RESPONSE TO IMPLANTATION AND PRE-OPERATIVE FINDINGS

Because of a paucity of conventional methods, some new parameters were explored. In addition, the effect of implantation on conventional disease features were noted. The parameters used will now be detailed.

Headache

This was a common symptom, being present in 14 of the 22 patients. It was found to be too vague and subjective for much reliance to be placed on this as an index of disease response.

Paraesthesiae

Tingling or pain, usually in both hands, was a more clear-cut symptom, and was found to be a fairly reliable indicator of disease activity where the symptom was severe and continuous before implantation. 12 of the 22 patients had this complaint before treatment. In some cases it was the major complaint, occasionally being very severe indeed. It invariably* ceased if there was an otherwise good response to implantation.

Sweating

This was assessed purely clinically. In the patients suffering from severe skin greasiness, improvement was evident in those having a good disease remission. This feature will not be further considered, nor used as evidence of disease activity.

Energy

This was noted from patient's statements. Again it was too subjective a feature to use in gauging disease response, but improvement in energy was quite striking in some patients having a good disease remission.

Acromegalic facies.

This was assessed by photography. Probably the observations of the doctor and others is more sensitive to small changes than photographs.

Visual fields

Although there were no patients with field defects before implantation, all were periodically checked subsequently by perimetry or Bjerrum screen examination.

* late addendum; one relapse.

Hand volume

This was measured as follows. The patient immersed the hand up to the wrist in a vessel filled with luke-warm water. The hand volume was given by the volume of water overflowing. Three measurements were made on each hand, and the mean noted. It was always possible to obtain a series of measurements agreeing within 10 ml. At first measurements were made from immersion up to a skin mark which was made on each occasion at the tip of the radial and ulnar styloids. Later, to improve reproducibility a tiny tattoo mark * was made at these two landmarks, and this provided a permanent level for immersion. A change of over 50 ml., which is well outside the random fluctuation of 20 ml. found from rapidly repeated serial measurements, is taken as a significant change.

Change in the position of the teeth

In a number of patients, the distance between the posterior teeth on right and left sides were measured serially. Diameters measured were from the buccal surfaces of the teeth, at their widest point, which was usually about 2 mm. from the gingival margin. In addition, serial plaster casts were made of the upper and lower teeth, and articulated by means of acrylic bite-impressions, and from these, a number of inter-dental diameters could be measured as well as the degree of prognathism. All the casts were taken in the Dental Department, Hammersmith Hospital. All measurements, clinical and of the models were made with the same vernier caliper.

The augmented insulin tolerance test (ITTa)

This test was suggested by Professor Russell Fraser as a possible parameter of acromegaly activity, arising from some personal observations during the standardisation of his original "conventional" insulin tolerance test (Fraser et al., 1941). In the original test, designed

* Tattooing was done by placing on the skin a tiny drop of 10% Indian Ink in water, and pricking through the drop into the skin with a fine needle. It is convenient, in making hand volume measurements, to have the patient sitting on a chair, and the vessel on a low stool at such a height that the hand could be immersed by thrusting it vertically downwards with the wrist and fingers in line with the forearm.

to identify hypopituitarism, an intravenous injection of 0.1 unit of soluble insulin per kilo body weight was given. For the augmented insulin tolerance test (ITTa), three times this dose was used, i.e. 0.3 u/Kg. Actually, 11.1 units per square meter body surface were given, being the same dose in an average sized adult.

As with all tests of carbohydrate metabolism, a standard intake of carbohydrate (300 grams daily) was ensured during the three days prior to testing. The test was done early in the morning, after an overnight admission, with fasting from 8 p.m. Special precautions were taken to have the patient relaxed and comfortably reclining. Although normal subjects and active acromegalics show different blood sugar values throughout the whole of the two hours after the insulin is given, the widest separation between normal and abnormal levels is found during the second hour. Hence, the test results can be expressed conveniently as an "insulin resistance index", being the sum of the blood sugars at 60, 90, and 120 minutes. At these critical times, duplicate specimens were obtained. The test is only applicable in non-obese subjects who have a normal fasting blood sugar level (under 90 mg.%)

The blood sugars which were estimated in the Hospital Routine Biochemistry Laboratory were nearly all done on a "Technicon" autoanalyser; the method is based on that of Hoffman (1937). From an analysis of 100 pairs of estimations in the range 50 mg.% to 180 mg.%, each member of a pair being from a separate blood specimen obtained from the same finger-prick, the standard error was found to be $\pm$ 3%, when duplicate sampling is used. The normal range for the insulin resistance index, based on tests done on 19 normal non-obese subjects was 62 to 142 mg.%. There was no skew distribution. The mean was 92 mg.%, and S.D. 22 mg.%, so a statistical range from the mean $\pm$ 2 S.D. is 46 to 136 mg.%. In actual fact, 95% of normal subjects gave values under 137 mg.%, so it is probably more correct to define an extreme upper limit of normal, to the nearest round number, as 145 mg.% with a borderline zone of 135 to 145 mg.%. These values, and some results in acromegaly have already been published (Fraser et al., 1962). Normal subjects always sustained

moderate hypoglycaemic symptoms for about half an hour, whereas untreated acromegalics and grossly obese subjects had none. This was a striking clinical difference.

In the acromegalics treated by pituitary implantation, the test was carried out before operation, and serially afterwards, in those in whom hypopituitarism had not been produced. Only one acromegalic studied was obese.

For the practical purpose of identifying acromegaly, all the test results from patients before implantation can be considered. There was a total of 17 different patients tested who had a normal oral GTT and were euthyroid both clinically and by I-131 testing. The range of the insulin resistance index results was 134 to 228 mg.%, with a mean of 173 mg.%. There was but one patient with a result (134mg.%) below the extreme upper limit of normal of 142 mg.%.

The 6 patients with test results of under 150 mg.% before implantation can be examined for other evidence of disease activity, in order to assess the significance of such small test abnormalities. Four of the six have been reassessed after implantation; two showed very striking regression of the acromegalic facies, while a third who had but a slight abnormality in her facial appearance, lost her paraesthesiae. Thus there were three patients with proof of active disease whose test index was just above, or just below the extreme upper limit of normal.

The prednisone glycosuria test (PGT)

This test was originally evolved for the detection of pre-diabetes, and the normal values and findings in various potential pre-diabetic states have been reported (Joplin et al., 1961). Blood sugars were again done on the autoanalyser, and urine sugars by a simple copper titration (King and Wootton, 1956). As used throughout the study of acromegalic patients, the test consisted of preparing the patient with a 300 gram carbohydrate diet for three days, and following an overnight admission, a standard 2½ hour oral glucose tolerance test (GTT) was

done to exclude chemical diabetes*, or renal glycosuria**. Then 20mg. of prednisone was given orally at noon, 4 p.m., and 8 p.m. Food was permitted during this afternoon period, up to 6 p.m. Urine was then collected from 10 p.m., to 6 a.m., and nurses took a finger-prick blood sugar at midnight and at 1 a.m. By 15/6/61 it was found that 29 of 30 normal subjects passed under 60 mg. sugar per hour during the overnight urine collection, and the mean of the midnight and 1 a.m. blood sugars was under 128 mg.%., in 9 normal subjects. All of 14 exceptionally mild diabetics, and about half of a population of 79 patients (infants of birth weight over 9 lbs. and diabetic relatives) in whom diabetes might be anticipated in spite of a normal oral GTT showed an overnight glycosuria of over 60 mg./hour, and half of these also had a mean night blood sugar of over 128 mg.%. Originally, a true glucose method with glucose oxidase was used for the urine sugars, and the upper limit of normal for the post-prednisone night collection was 25 mg./hour.

The test was done routinely before implantation in the non-diabetic acromegalics, and serially afterwards, when readmitted for assessment so long as steroid-dependency had not been incurred.

To assess the significance of this test as an index of acromegaly activity, the test results of the pre-implant tests done in 9 patients with a normal oral GTT can be examined. Six were abnormal. However, the pre-implant tests in three patients were normal, yet the active nature of the disease in two was later shown by their obtaining a striking clinical remission after implantation. Thus, it would appear that most, but not all active acromegalics have an abnormal PGT.

The change of the PGT from abnormal to normal after implantation in non-diabetic acromegalics confirms the value of the test in showing a diabetic tendency that is too mild to produce an abnormal oral GTT. In addition, the relative sensitivities of the two parameters of the test response, the overnight glycosuria and midnight blood sugars can

* Chemical diabetes was diagnosed when the fasting blood sugar exceeded 100 mg.%, and/or the 1½hr. and 2½hr. blood sugars exceeded 140 and 95 mg% respectively.

**Renal glycosuria was defined by collecting urine during the 2½ hours of the GTT. Normal subjects, where the blood sugars are below 90, 160, 140, 120, and 95mg% (fasting 1, 1½, 2, 2½ hrs.), pass under 80 mg. of sugar/hr.; subjects who frequently have glycosuria when fasting, pass much more than 80mg./hr. during a GTT with normal blood sugar.

be compared. There were eight tests with overnight glycosuria of over 60mg./hr., whose blood sugars were measured simultaneously; six had high blood sugars. Among the nine patients with normal glycosuria, there were no instances of a high blood sugar.

Radiological thickness of the metacarpal cortex.

Most patients had radiographs of the hands before and serially after implantation, from which cortical thickness could be measured and compared.

Radiological pituitary fossa size.

Plain radiographs were taken on the Lysholm skull table in the lateral, antero-posterior, and 25° tilt fronto-occipital views, before implantation and approximately 6-monthly afterwards. In addition, periodical examinations by lateral tomograms were made. Thus, the radiological pituitary fossa size could be serially observed.

Before implantation, satisfactory x-rays of the pituitary fossa were obtained in 20 acromegalic patients. The abnormalities found are detailed in Table XVIII.II. It is evident that the most sensitive single measurement is the pituitary fossa area, using the smallest visible contour; an abnormally large area was shown in 16 of the 20 patients. Three of these patients had a perfectly obvious second contour, whose area was abnormally large. Thus, there was but a single patient (case M.Fo.) whose fossa area was normal and also had no second contour; indeed, there was no radiological abnormality whatsoever in this patient's pituitary fossa and the width of the waist of the dorsum sellae (17 mm.) and of the fossa floor (16 mm.) were also well within the normal range.

A useful confirmation of the significance of a double contour in the lateral film is provided in a straight antero-posterior film showing the fossa floor. In half of the cases where the fossa floor was clearly visible in the antero-posterior film, it was found to be abnormally sloping. More often, the sloping part was at one side, rather than forming a central depression.

Lateral tomographs of the fossa gave much the same information as did a plain lateral film combined with an antero-posterior film. Tomographs were taken in 18 cases, and in 14 an abnormality indicating a localised expansion were shown. When the plain films of the 14 were

RADIOLOGICAL ABNORMALITIES* OF THE PITUITARY FOSSA BEFORE IMPLANTATION (20 PATIENTS)

		Extreme upper limit of normal	No. acromegalics observed	% cases clearly abnormal	Range observed	Any normal values
PLAIN LATERAL RADIOGRAPH	Fossa area (smallest contour)	145 sq.mm.	20	75%	106–330 sq.mm.	106, 125, 140, 145
	Fossa depth (smallest contour)	13 mm.	20	20%	10–25mm.	10(5),11(4),12(5), 13(1), 8(1).
	Fossa length (smallest contour)	16 mm.	20	45%	12–25mm.	12(1),13(5),14(1), 15(3),16(1).
	Double contour	-	20	75%	-	-
	Irregular contour	-	20	90%	-	-
	Anterior clinoids undercut	-	20	30%	-	-
	Dorsum thin	-	20	35%	-	-
	Posterior clinoids eroded	-	20	50%	-	-
PLAIN A-P	Fossa floor irregular in ant-post.view	-	18	45%	-	-
LAT. TOMOGRAMS	Double contour	-	14	80%	-	-

* All measurements are quoted exactly as obtained by direct measurement on the radiographs.

inspected, all but one showed a definite double contour. The value of lateral tomographs lies in the confirmation of the presence of an expanded fossa in a known sagittal plane, and shows the variation in fossa shape in successive planes, which is vital to implant planning.

Measurements of serum and urinary calcium and serum inorganic phosphate.

In most patients, measurements of these three indices of calcium metabolism were made before implantation. The urinary calcium measurements were recorded as the mean of the three 24-hour collections made on the 4th, 5th and 6th days of a diet which was normal but omitted milk and milk products, and hence would contain under 25 mEq. calcium per day. In most cases, two or more measurements of serum calcium and inorganic phosphate were made and the mean values will be quoted. All the pre-implant levels are shown on Table XVIII.III.

TABLE XVIII.III.

PRE-IMPLANT ESTIMATIONS OF SERUM AND URINE CALCIUM AND SERUM INORGANIC PHOSPHATE

	Upper limit of normal*	No. patients tested	No. patients with high values	Abnormal values
Serum Ca. (mEq./l.)	5.4	21	Nil	Nil
Serum P (mEq./l.)	2.6	23	1	2.9
Urine Ca. (mEq./day)	15	15	7	16,17,17, 18,29,31, 37

* see Chapter XII.

It is evident that the serum calcium was always normal. Inorganic phosphate was elevated in only one patient, and could not therefore provide evidence of "activity" of acromegaly; there were, however, a number of patients with levels just below the upper limit of normal. On the other hand, calcuric patients who had excellent clinical remissions were re-tested and in both the urinary calcium excretion had fallen to normal (29 to 8 mEq./day; 16 to 9 mEq./day).

SPECIAL ASPECTS OF THE IMPLANTATION METHOD IN ACROMEGALY

Two aspects peculiar to tumour implantation were the planning on a basis of lateral pituitary fossa tomograms as well as plain radiographs (because of frequency of more than one pituitary fossa outline on plain lateral radiographs), and the problem that arises when a cyst is encountered.

An example of an intra-pituitary cyst (case B.Ke.) is shown in Fig. XVIII.I. A cyst was encountered in 6 of 22 acromegalics in whom implants were attempted. In 3 cases, the cysts were so large that either no implant was attempted, or a few short seeds were merely dropped on to the cyst floor. It was later found that if the implant was planned to include very long Y-90 rods, these would span a cyst, and remain fixed.

Irrespective of the dose plan, all implants in acromegalic patients were done by a single needle-hole into the fossa on each side of the midline. Pituitary biopsy was much easier to obtain from tumour tissue than from normal gland; there was no special tendency to bleeding from the biopsy needle.

Because of the greater risk of pituitary infection when implanting tumours, it was the practise to begin the streptomycin and sulphadiazine cover 24 hours before the operation, and to continue these for the usual 5 days post-operatively. No steroid cover was given, with the exception of a few patients given an intentional ablation dose as a second implant procedure; for this purpose, the plan was to give a dose of 100,000 rads at the diaphragma sellae from Y-90 alone.

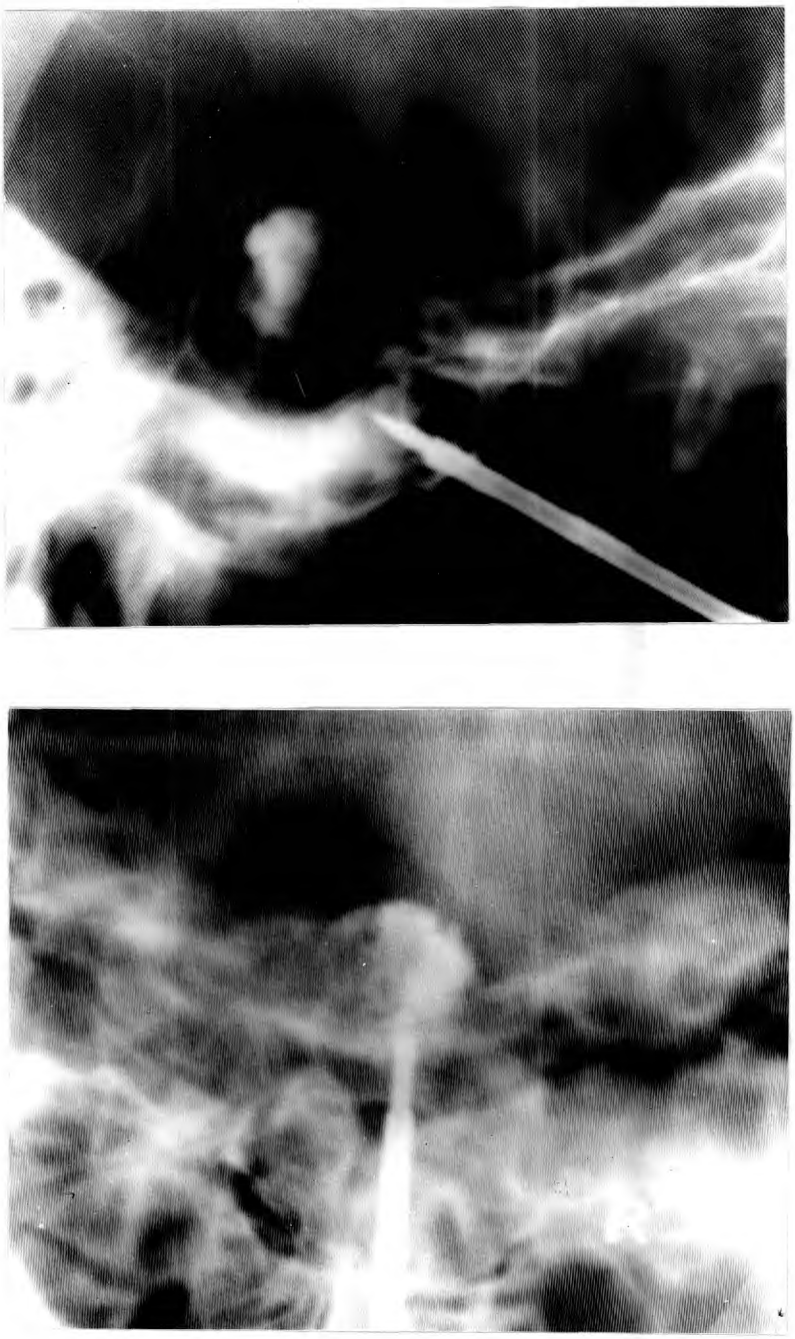


Fig. XVIII.I. An intra-pituitary cyst (case B.Ke.) was demonstrated by injecting 40% "Hypaque". As the cyst was very large, and extended well above the normal level of the diaphragma sellae, implantation of radioactive material was not done.

RESULTS

The effect of initial Au-198 implantation upon acromegaly (Table XVIII.II)

The seeds were introduced through two needle-holes, the plan being to use activities which would give the entire tumour periphery at least 10,000 rads, provided this dose was not exceeded at the normal radiological position of the diaphragma sellae. One patient died (see later) soon after the operation, so effects of implantation are based on the remaining 16 patients. These are detailed in Table XVIII.II. For each parameter, the frequency of improvement is shown as a proportion of the patients assessed. It is evident that most showed symptomatic improvement, and about half showed regression of the acromegalic facies. Many also showed a reduction in bone overgrowth, and improved tests of carbohydrate metabolism. An example of a patient undergoing a good remission is described in detail in Appendix I. (case S.Ri.). These improvements were obtained at the expense of incurring hypopituitarism in two patients (following pituitary infection).

A further patient (case A.Wy.) had an initial implant using both Y-90 and Au-198, each being planned to give the gland periphery 5,000 rads. She obtained no improvement in any parameter of disease activity.

Effect of re-implantation on acromegaly (Table XVIII.III)

Eight patients had second implants of various types because of inadequate disease response to the first. The effect of the second implant is shown in Table XVIII.III. It is evident that most patients responded to re-implantation.

Two further patients had atypical second implants. Case S.Cl. had a second implant of Y-90, aiming to give the diaphragma sellae 10,000 rads, purely as treatment of tumour expansion, suspected (incorrectly) because of the development of bilateral field defects. As the disease was in satisfactory remission before this second implant, she does not appear in Table XVIII.III. A second atypical re-implant was done in patient H.La., with a dose plan of only 1,000 rads at the diaphragma sellae from Y-90 alone. No improvement occurred in what was very active disease.

TABLE XVIII.II

EFFECT OF GOLD-198 IMPLANTATION ON ACROMEGALY IN 16 PATIENTS (DOSE:10,000 rads to diaphragma sellae).

	Parameter	No. of patients
CLINICAL	Headache lost or much improved	8/10
	Paraesthesiae lost	5/7
	Facies regressed	6/14
	Both hand volumes fell by >50ml.*	1/14
	Interdental diameter* decreased by 0.4mm.	2/3
	Became dependent on thyroxine or cortisone	2/16
TESTS	ITTa became normal	7/12
	Prediabetes lost (PGT)	2/4
	Diabetes lost	2/3
	Metacarpal cortical thickness** diminished	1/7
	Pituitary fossa size* or shape changed	0/13

* only considered patients followed for over 1 year

** only considered patients followed for over 2 years.

Overall assessment of response to implantation of the whole series (Fig.XVIII.

All the patients with enough serial data for assessment are shown in Fig. XVIII.2. The response to the various implants was assigned to three categories:-

"Satisfactory response": definite regression of the acromegalic facies, loss of paraesthesiae, and conversion of an abnormal ITTa, or PGT to normal, or loss of diabetes mellitus.

"Partial response": some of the above improved, but not all.

"No improvement": none of the above improved.

It can be seen from the summary diagram in Fig. XVIII.2 that out of

TABLE XVIII.III

EFFECT OF RE-IMPLANTATION ON ACROMEGALY IN 8 PATIENTS

	Parameter	Y-90 only; 100,000 rads to diaphr. (4 patients)	Y-90 only; 10,000 rads to diaphr. (2 patients)	Au-198 and Y-90 5,000 rads to diaphr. from each (2 patients)	Effect of all re-implants
CLINICAL	Headache lost or much improved	4/4	nil	0/1	4/5
	Paraesthesiae lost	2/2	nil	0/1	2/3
	Facies regressed	3/4	1/1	2/2	6/7
	Both hand volumes* fell by >50ml	2/4	1/2	1/2	4/8
	Interdental diameter* decreased by 0.4mm.	1/2	nil	nil	1/2
	Became dependent on thyroxine or cortisone	2/2	0/2	2/2	4/6
TESTS	ITTa became normal	3/3	nil	nil	3/3
	Prediabetes lost (PGT)	2/2	nil	nil	2/2
	Diabetes lost	nil	nil	1/1	1/1
	Metacarpal cortical thickness** diminished	3/3	0/1	0/1	3/5
	Pituitary fossa size or shape changed*	0/4	0/2	0/1	0/7

* reported only on patients followed over 1 year

** reported only on patients followed over 2 years.

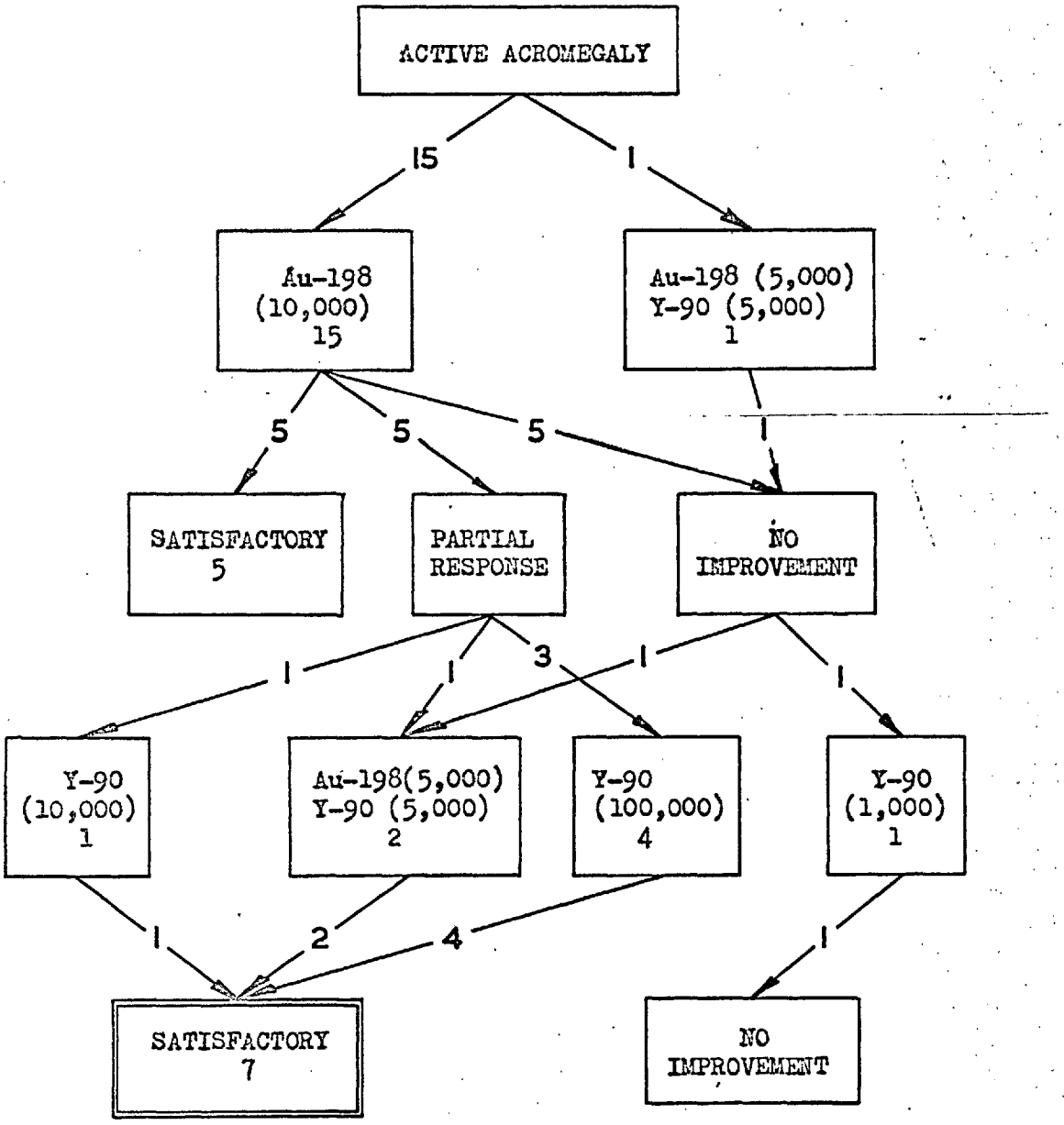


Fig. XVIII.2.- Effect of various types of implant. Figures in brackets are the planned doses, in rads, at the "diaphragma sellae".

the 16 assessed after an initial implant of Au-198 alone, or Au-198 plus Y-90, planned to give the diaphragma sellae 10,000 rads, only five obtained a "satisfactory" result. Of the eight re-implanted because either there was no improvement after the first implant, or because there was but a partial response, all seven who were given a dose of at least 10,000 rads at the diaphragma sellae, obtained a satisfactory result.

Therefore, out of an initial series of 16 patients whose response was subsequently assessed, (7 had already failed to respond to a total of at least 3,500 rads delivered by external irradiation), 12 obtained an entirely satisfactory disease-remission after one or two implantations, and 4 remained totally unimproved.

Hormone dependency

Hormone dependency was incurred in a total of 7 of the 16 patients in Fig. XVIII.2. All obtained a satisfactory disease response. Thus, half of the patients whose acromegaly remitted also became hormone dependent. Of the 7 patients who became steroid dependent, 4 had sustained a post-operative meningitis syndrome, so in these patients at least, infection was probably responsible. The remaining 3 patients had no such clinical episode; in all 3, the hypopituitarism had followed re-implantation with Y-90 alone, the planned dose to the diaphragma sellae being 100,000 rads in two, and 10,000 rads in one.

Rapidity of response.

The time of clinical response to implantation could be examined from those responding patients in whom note was made of the commencement and completion of improvement. The results are shown in Table XVII.IV. Improvement in paraesthesiae occurred early (immediately after implantation in two patients), while regression of facies was not usually evident until later.

The ITTa results indicated regression still occurring after three to six months (Fig. XVIII.3). In six patients responding to implantation, this test was done at three to six months post-implant, and again within the next three years. In all six patients there was a further drop, when the test done at three to six months was compared with the test done after a year (data given in Fig. XVIII.6).

TABLE XVIII.IV

THE RAPIDITY OF IMPROVEMENT OF THE ACROMEGALIC FACIES AND PARAESTHESIAE FOLLOWING IMPLANTATION

	Total no. cases noted	First improvement noted (weeks post-implant)	Final status achieved (weeks post-implant)
Facies	11	2-32 (mean=12)	2->96 (mean=>44)
Paraesthesiae	4	1 to 2	1 to 36

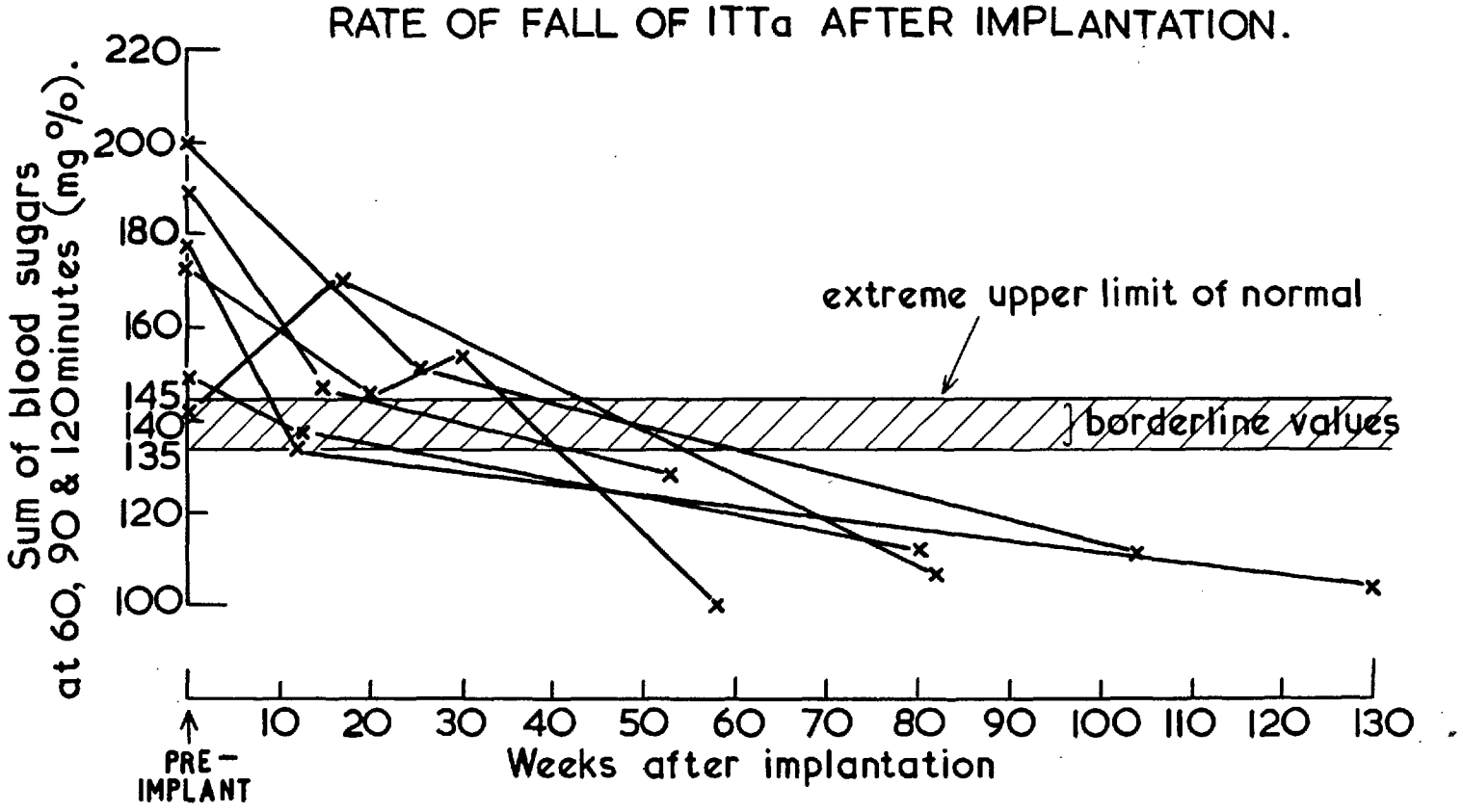


Fig. XVIII.3. These are the serial (post-implant) tests done in 6 patients in whom the final test result was lower than before implant.

FURTHER RESULTS OF THE EFFECT OF PITUITARY IMPLANTATION ON CERTAIN CLINICAL PARAMETERS AND TEST MEASUREMENTS

Headache

This symptom, although important to the patient, was difficult to evaluate. Altogether there were 14 (64% incidence) patients with headache before implantation, for 13 of whom follow-up data was obtained. In 11, headache either substantially improved, or completely disappeared. Those patients who obtained a satisfactory overall response to implant, lost or nearly lost, their headache.

The effect of implantation on interdental diameters (Table XVIII.V: Figs. XVIII.IV. and XVIII.V).

Method of study. Serial measurements were made (a) clinically, by the same vernier caliper, of the distance between the buccal surfaces of the lower canines or pre-molars, and (b) by serial plaster casts made of both jaws together with acrylic bite-impressions. These plaster casts are extremely accurate, and distances between teeth can be measured with precision, as identical points on the tooth surfaces can be selected for the serial measurements in a given patient. In no case was a dental diameter measured from teeth adjacent to an extraction, old or recent; neither were any measurements made using the eights. By articulating the upper and lower casts with an acrylic bite-impression, it was possible in many cases to make accurate measurements of the degree of prognathism. Apparent changes in this measurement could be further checked by attempting to articulate the last set of casts by means of the first bite-impression, and noting the site on the jaw at which the changes had occurred.

When the serial measurements made clinically were compared with the serial measurements on the dental models, a close agreement was found. No patient's progress was differently gauged by the two methods of measurement.

Results The results of the clinical measurement are shown in Table XVIII.V. Six patients had serial measurements of the lower canine or

pre-molar diameters for 12 to 38 months after a first implantation. There were three in whom there was a change of over 0.4mm; only two were assessable on clinical grounds with respect to acromegaly remission, and both indeed showed a remarkable regression of the facies and loss of finger paraesthesiae. Measurements across the upper teeth were made in three patients for 13 to 26 months post-implant. The only change recorded was in one of the above excellent responders.

TABLE XVIII.V.

CHANGE IN CLINICAL MEASUREMENTS OF INTERDENTAL DIAMETERS

	Caliper measurements (mm.)	
	Pre-implant	Post-implant
Lower* canine or pre-molar	32.4	31.4
	42.0	41.5
	56.4	56.0
	41.6	41.6
	35.5	35.4
	34.6	34.6
Upper canine**	35.6	34.7
	37.2	37.1
	44.6	44.5

* followed 12-38 months

** followed 13-26 months.

The changes found with the dental casts are shown in Figs.XVIII.4a and XVIII.5. All the measurements in patients with a good* overall response are shown. It is evident that in some patients a diminution in inter-dental width of both the lower and upper jaws occurred with acromegalic regression,

* clinical regression of acromegalic facies, loss of paraesthesiae (if present), and a normal ITTa and PGT.

CHANGE IN DENTAL MODELS AFTER IMPLANTATION IN PATIENTS WITH A GOOD GENERAL RESPONSE.

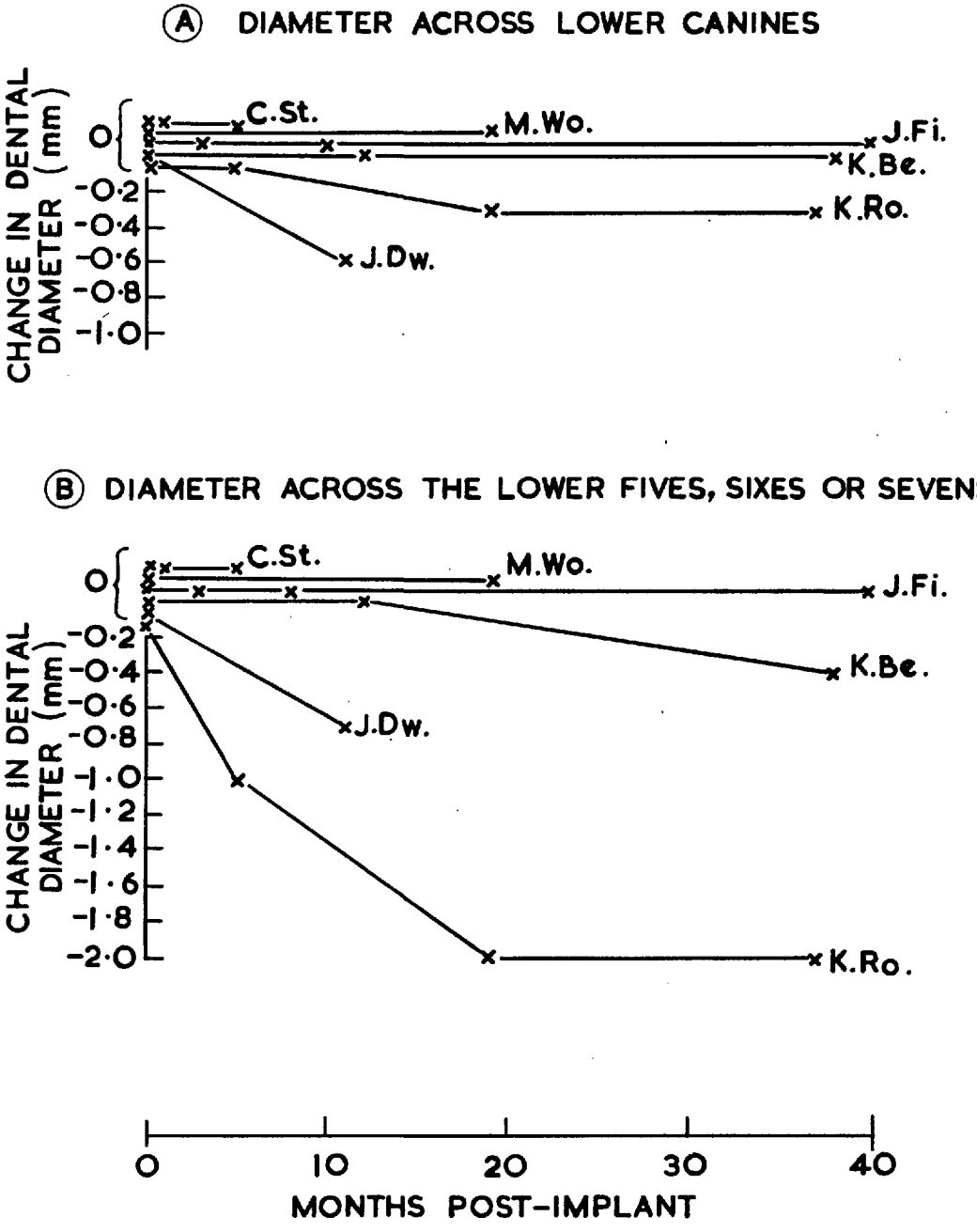


Fig. XVIII.4.- Change in interdental diameters of models of lower jaws occurred in 3 of 6 patients followed for over 5 months after effective implantation.

CHANGE IN DENTAL MODELS AFTER PITUITARY IMPLANTATION IN PATIENTS WITH A GOOD GENERAL RESPONSE.

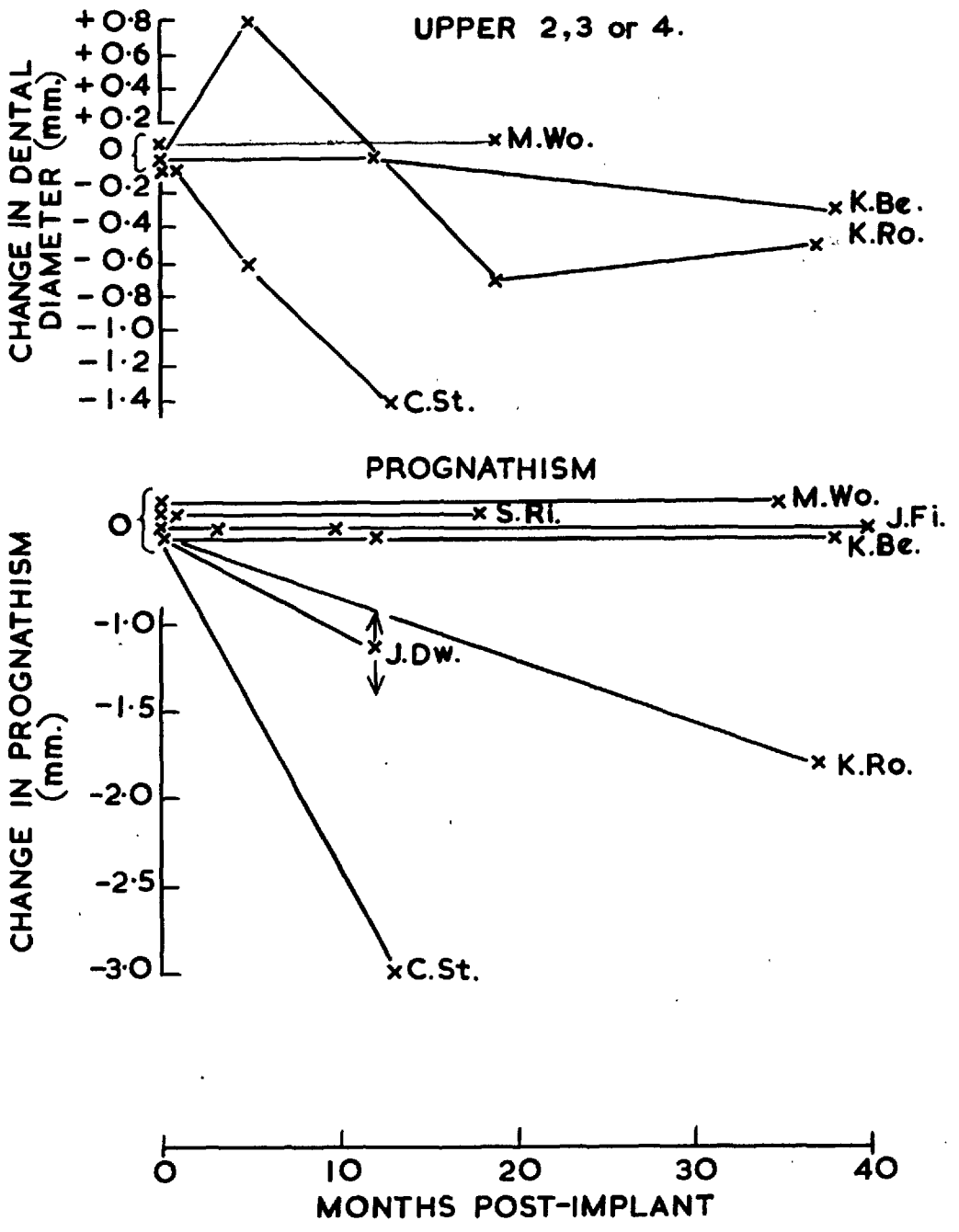


Fig. XVIII.5 - Regressions were found in both upper jaw dental diameter and prognathism. The measurement of J.Dw. is of doubtful accuracy.

and that the extent of regression in the lower jaw was greater with the more posterior teeth than with the canines. Dental regression was first seen at five months and continued up to the twentieth month.

Measurement of prognathism might be suspected of variability, but it can be seen in Fig. XVIII.5., that there was no random variation.

If only the measurements of jaw diameter in the seven different patients in Figs. XVIII.4 and XVIII.5 with a good overall clinical response of the disease are considered, four showed dental regression.

Patient K.Ro. showed the most striking changes, and can be taken to illustrate the agreement between the various measurements on the dental models. The regressions at 37 months were as follows: lower canine, 0.3mm., lower sixes, 2.0 mm., upper fives, 0.5mm., prognathism 1.8 mm. She was well aware of the decreased spacing between the lower incisors.

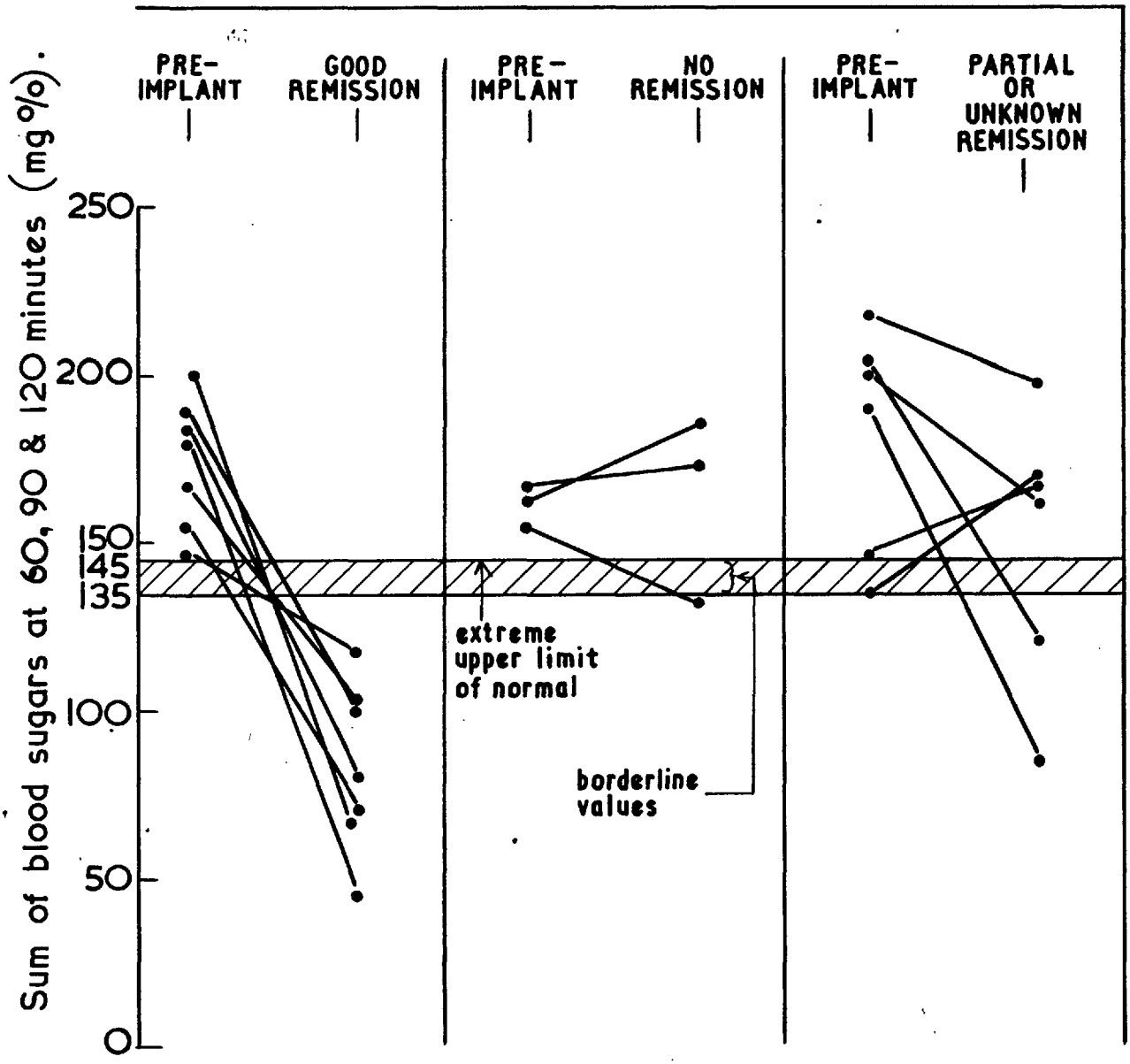
There were two patients who showed no general response to implantation, in whom serial dental models had been made. The periods of follow-up were 13 and 25 months respectively. One showed a further widening of the lower canine diameter of 0.2mm., and the other showed no change.

The effect of implantation on the Augmented Insulin Tolerance Test (ITTa) (Fig.XVIII.6.)

The results of this test, done before and after pituitary implantation, are shown in Fig. XVIII.6. The patients were classified according to the clinical regression of facies and paraesthesiae after implantation. Patients having two implants may therefore be represented twice in the diagram.

If the post-implant values of the 7 patients with a good clinical response are first considered, it is seen that all fell to well within the normal range; fortuitously, all these patients had a raised value before implantation. However, among the three patients in the next group with no clinical remission at all, there is one patient who did obtain a normal value after implantation. Similarly, in the third group, there were two patients whose tests fell from clearly abnormal to clearly normal,

EFFECT OF PITUITARY IMPLANTATION ON THE AUGMENTED INSULIN TOLERANCE TEST IN ACROMEGALY, SHOWN CORRELATED WITH CLINICAL REMISSION



[illegible] – [illegible] on their clinical response, i.e. regression of acromegalic facies and loss of anaesthesiae.

yet in fact, these two patients showed but slight clinical remissions, and subsequently obtained a striking remission after re-implantation.

It would thus appear that the obtaining of a normal ITTa after implantation is not of itself an adequately stringent single criterion of a successful operation, if a clear clinical remission is adopted as the ultimate goal.

To further compare the test results with response to implantation, all of nine tests done after an implant leading to a good clinical remission can be considered. As well as the patients in Fig. XVIII.6, there were tests done on two patients who had not also been tested before implantation. The mean test value for the nine patients in good clinical remission was 88 mg.%, with a range of 45 mg% to 126 mg%. Thus, a normal ITTa has invariably accompanied a good clinical remission. There was no instance of weight loss after implantation which might alternatively explain the drop in the insulin resistance index.

The effect of implantation on the prednisone glycosuria test (Fig.XVIII.7).

Most acromegalics with normal thyroid and adrenal function were tested in this way when admitted for assessment before or after implantation. In most cases, as well as collecting the post-prednisone overnight urine for sugar estimation, blood sugars were taken by finger-prick at midnight and at 1 a.m., and the mean recorded. In all cases, a standard oral GTT was done the day before the PGT so as to identify any patients with chemical diabetes.

In Fig. XVIII.7 is shown all the results. Where a patient had more than one post-implant test done, the last is shown. No tests done within three months of operation are included. In patients with clinical diabetes, the test was not usually done, but so as to give a graphic comparison with their post-implant tests, the results have been plotted, as would be expected, as "over 250 mg./hr.", and identified as "D.M.".

The tests in the six acromegalics in good clinical remission can first be inspected. With a minor exception, all obtained normal test results after implantation, both on urine and blood sugar criteria, whereas two had clinical diabetes before operation.

EFFECT OF PITUITARY IMPLANTATION ON THE PREDNISONE GLYCOSURIA TEST IN ACROMEGALY, & CORRELATED WITH CLINICAL REMISSION.

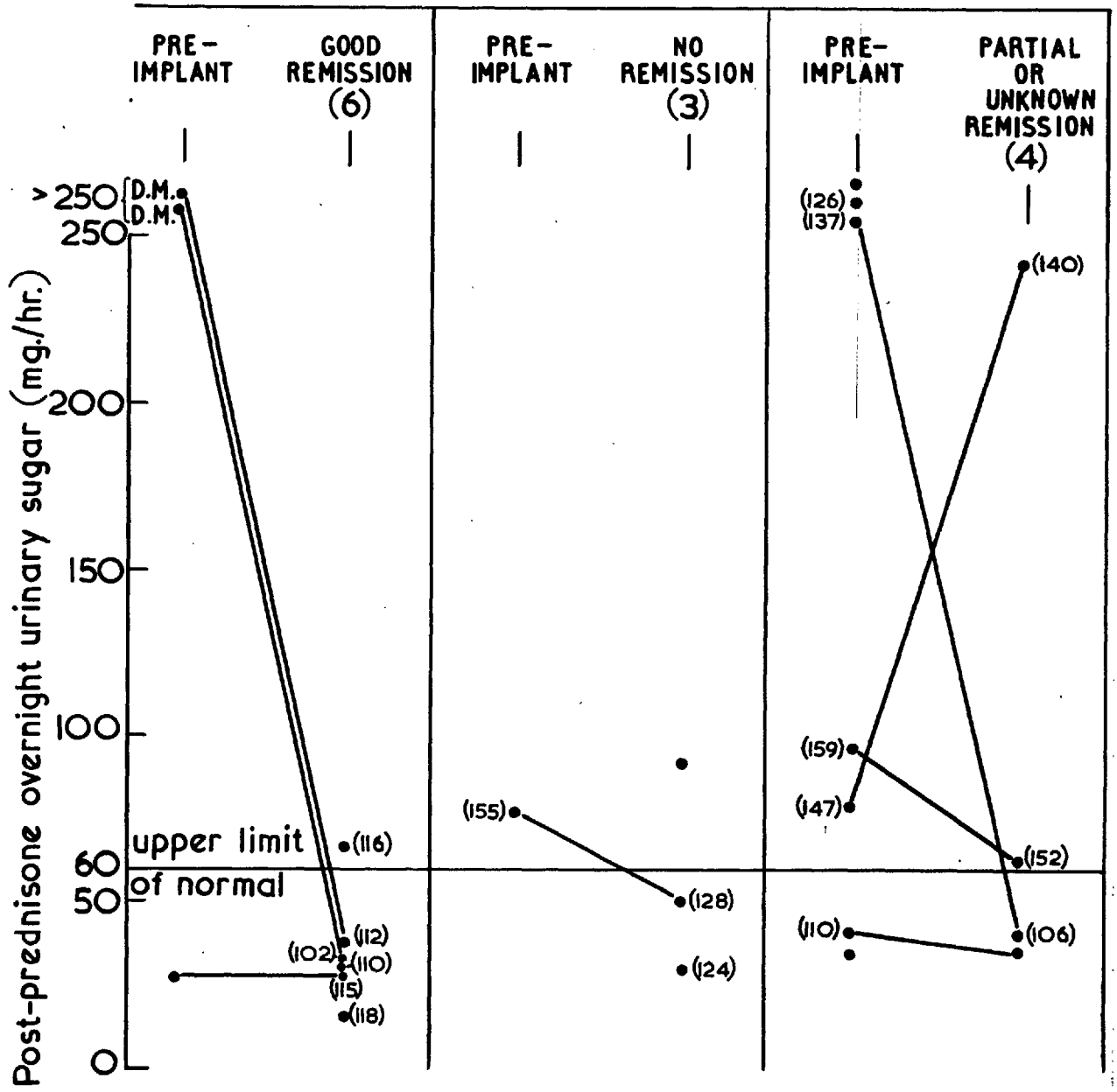


Fig. XVIII.7 – Patients were classified entirely on their clinical response, i.e. regression of acromegalic facies and loss of paraesthesiae. Midnight blood sugars are shown in brackets.

There were three who showed no clinical remission after implantation, yet two of these patients obtained normal post-implant tests.

In the group of four patients whose clinical response to implantation was but "partial or unknown", there were two patients who did in fact obtain a partial clinical remission. Both were tested both before and after implantation; in one, the test remained abnormal, but in the other (who later had a striking response to re-implantation) the test became normal.

Summarising the above results of tests done after implantation, there were three patients who either showed no clinical regression, or partial regression, yet had normal PGT results. There was a total of six tests done after implantation in patients who obtained a good clinical remission; all had both urine and blood sugars measured, and with a marginal exception, all values were entirely normal. Thus, in non-diabetics, the achievement of a normal PGT was an invariable consequence of an otherwise effective operation, but it is only a minimal criterion of a successful operation.

The effect of pituitary implantation on the radiological appearance of the metacarpal bones (Fig. XVIII.8.).

Serial radiographs of the hands were taken for at least two years after implantation in ten patients. The bones showing change were the metacarpals, the most striking being in the second and third. The alteration consisted of a reduction of the thickness of the cortical bone, due to widening of the medulla (e.g.case K.Ro.,Fig. XVIII.8).

Measurements of thickness of the metacarpal shaft and medulla were made in both hands of the ten patients with serial x-rays. Four patients showed a change which was evident both on inpsection and capable of measurement, consisting of widening of the medulla by at least 1.0 mm., without any change in the external thickness of the metacarpal shaft. It was present to a similar extent in both hands. These measurements probably underestimate the degree of change, because the medullary surface of the cortex in the untreated state was a sharp line, which

changed post-operatively into an irregular line due to a finer trabecular structure, but measurement of the width of the medulla was made from the innermost edge in this irregular boundary zone. The earliest change was seen at 18 months after implantation, and regression continued to proceed thereafter up to the time when the last film was taken (42 months).

All four patients showing metacarpal changes had a striking clinical regression, but there were four others with clinical regression who showed no obvious change in the metacarpal x-rays.

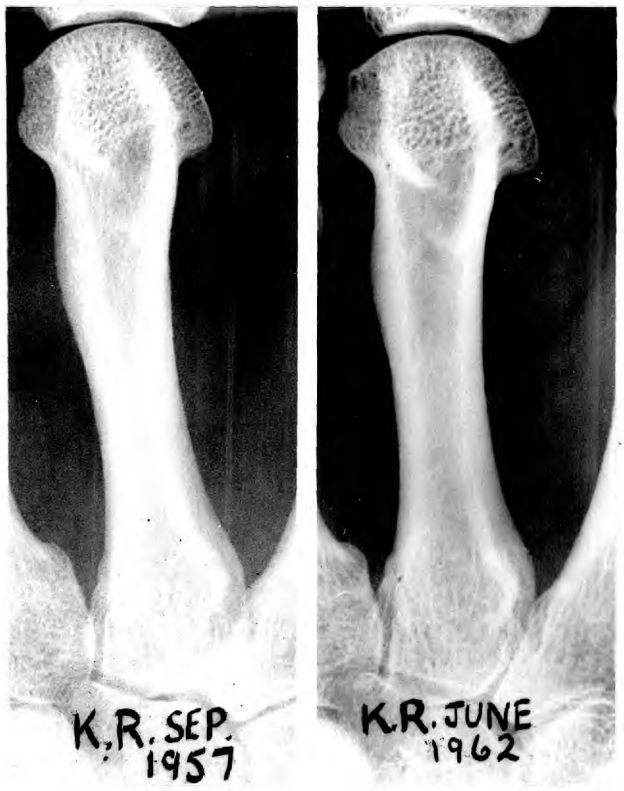


Fig.XVIII.8 – Case K.Ro. The effect of pituitary implantation in inducing thinning of the metacarpal cortex is seen. The first radiograph was taken before the first (ineffective) operation, and the second was taken two years after the second (effective) operation.

The radiological appearance of the pituitary fossa after implantation.

After implantation, satisfactory lateral radiographs of the fossa were obtained in 13 patients covering post-operative periods of 13 to 50 months. A total of 34 "patient-years" was thus covered. There was no instance of further radiological expansion of the fossa shown either on serial measurements of fossa area, or on measurements of fossa diameters. Special care was taken to select the same fossa contour for serial measurements in a given patient.

Effects of implantation on some miscellaneous features of acromegaly.

Two hypercalcuric patients who were re-tested after implantation had excellent clinical responses, and in both the urine calcium loss fell to normal (29 to 8 mEq./day; 16 to 9 mEq./day).

There were three patients with the associated features of Graves' disease or pigmentation, or narcolepsy.

Patient K.Ro. presented with Graves' disease, which had recurred following partial thyroidectomy, along with pretibial myxoedema. Pituitary implantation led to striking regression of the acromegalic facies and loss of paraesthesiae, but without improvement in the Graves' disease, which required therapeutic I-131 treatment. The pretibial myxoedema and eye signs did not regress after implantation, but did subside a year after she became euthyroid; implantation had not caused hormone dependence, and she continued to menstruate normally.

Patient M.Wo. presented with progressive acromegaly and marked generalised skin pigmentation. The first implant with Au-198 had little effect, either on the acromegaly or on the pigmentation. A second implant, using Y-90 giving a dose at the tumour periphery of 100,000 rads, rendered her hormone dependent, and she had a striking regression of the acromegalic facies and finger paraesthesiae. The abnormal pigmentation had disappeared by four months after the second implant. Pituitary biopsy showed that the tumour was almost entirely of eosinophils. Adrenal function had been shown to be normal pre-operatively and also after the initial Au-198 implant, in that a water diuresis test gave a 4-hour excretion of over 80% of a litre load, and urinary 17-KGS averaged

8mg./day in four collections; also, no steroid cover was required for the first operation. Although Davidoff (1926) found a 40% incidence of pigmentation in his large series of acromegalics, it would seem unlikely that really deep pigmentation as found in the present patient is at all common. She is unique in the author's experience of 33 acromegalic patients. It would seem likely that the tumour was secreting an abnormal quantity of melanophore-stimulating hormone in an analagous way to the postulated prolactin excess causing lactation (in 4% of cases, Davidoff, 1926; 2% cases, Gordon et al.,1962).

COMPLICATIONS FROM PITUITARY IMPLANTATION FOR ACROMEGALY

(TABLE XVIII.VII)

Complications comprised a meningitis-like syndrome, C.S.F. leakage, visual defect, and diabetes insipidus. The incidence of these is given below in Table XVIII.VII. In the upper half of the table, results are presented according to whether the implant was the initial one, or a re-implant. In the lower half of the table, results in the same patients are analysed according to whether Au-198 sources were used.

TABLE XVIII.VII

COMPLICATIONS FROM PITUITARY IMPLANTATION FOR ACROMEGALY

	No. operations	Meningitis syndrome	C.S.F. leak	Visual defect	Required pitressin	Death due to implantation
*First implant	22	6	1	2	1	1
Second implant	10	2	3	1	2	0
Yttrium-90 only	8	1	1	0	1	0
*Gold-198 alone, or with yttrium-90	24	7	3	3	2	1

* includes one operation where no sources were implanted

It is evident the commonest complication was a meningitis syndrome, occurring in about a quarter of all implants, and liable equally in first implants and second implants. C.S.F. rhinorrhoea seemed more liable in second implants. There is possibly less hazard with Y-90 implants than when Au-198 is used. These various complications will now be considered in detail.

Meningitis syndrome. There were a total of eight patients suffering this complication out of a total of 32 operations. It consisted of

moderate fever, neck stiffness, severe headache; in one instance there was papilloedema. Usually it responded within 24 hours to an effective antibiotic. The onset of a first attack was between 12 hours and 21 days after implantation, but usually in the first week. In no case did a first post-operative attack follow the onset of a C.S.F. rhinorrhoea. A second attack occurred in a total of four patients, in one of whom (case V.Sp.) a number occurred and constituted a grave disability. Thus, recurrence of meningitis occurred in half the patients affected.

The C.S.F. culture was a deceptive investigation. Pathogens were only grown in two patients. In one patient (L.We.) with a clinical meningitis syndrome, the C.S.F. was not only sterile, but also biochemically and cytologically normal, yet she died of what appeared clinically to be a combination of meningitis and steroid deficiency. Antibiotics had been given only intermittently, and steroids not until the terminal crisis. At autopsy, the pituitary tumour was practically completely liquified, being converted into a large pus-filled sac (see Fig.XVIII.9). There was no sign of generalised meningitis. There can be little doubt that this meningitis syndrome was often on an infective basis, judging from its prompt subsidence on the administration of antibiotics.

Postoperative meningitis occurred in spite of the operative "cover" with sulphadiazine and streptomycin in six cases, yet resolved in all but one case when chloramphenicol and penicillin were added. Of the four patients with a second attack of meningitis, all occurred within six months of implant. These recurrences had occurred in spite of prolongation up to two months of tetracycline or sulphadiazine treatment for the first attack. No recurrence occurred while the patient was actually having antibiotics. It would appear wise therefore to continue antibiotics for three months after a first attack, on the assumption that there is a residual intra-pituitary infection which otherwise may persist for up to six months before flaring up.

C.S.F. rhinorrhoea. There was a total of four instances in 32 operations. The onset was between the 7th and 42nd post-operative day. It subsided in a few days in two patients; in one it subsided spontaneously,

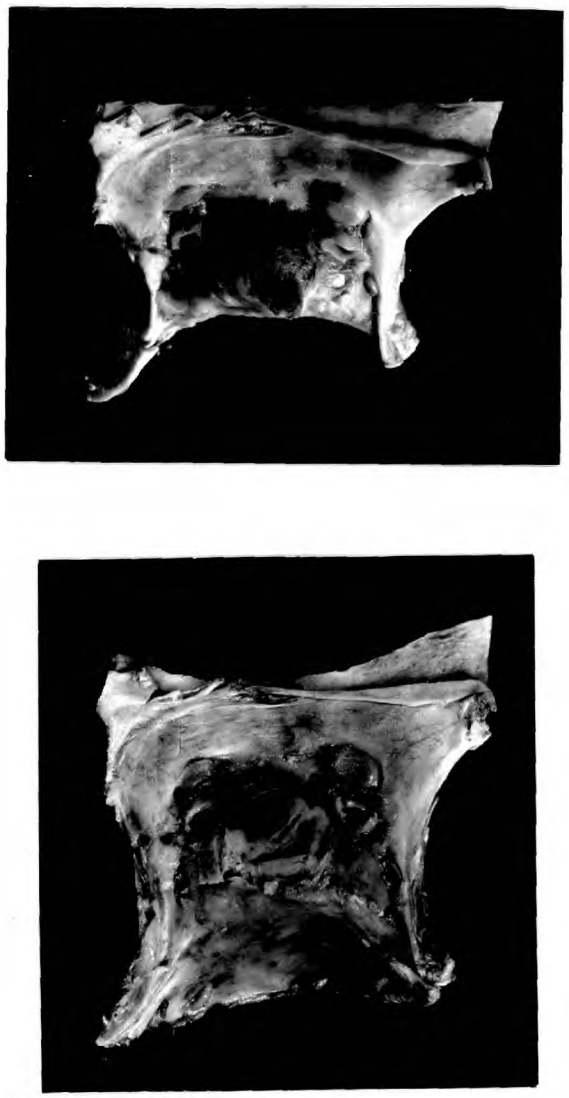


Fig.XVIII.9. Autopsy photographs of the pituitary tumour in case L.We. Implantation of gold-198 had been done 13 days before death. Above is seen the bulging tumour. Below is seen the appearance after the top of the tumour had been sliced off. The tumour had become a pus-filled abscess.

and one after 10 days of bed rest, lying supine with the foot of the bed elevated. In the other two patients, a screw was inserted, but only arrested the leak in one, so that the other required a plastic muscle graft to be inserted from a nasal approach by a highly skilled E.N.T. surgeon. Two of these four patients sustained an attack of meningitis in association with the leak.

Visual defect. No patient had a visual field defect before implantation. Three implants were followed by a visual field defect. The first was case V.Sp., who had numerous attacks of meningitis. The defect was noticed by the patient seven months after a second implant which was of mixed yttrium-90 and gold-198 seeds, planned to give the diaphragma sellae a total dose of 10,000 rads. There was unilateral acuity loss, and an upper nasal field defect on that side. Craniotomy was undertaken in the belief that there must be an expanding tumour, but in fact it was found that there was virtually no pituitary remnant, and that the chiasma had been carried down by adhesions into a voluminous empty sella.

The second case (case B.Ke.) had a large pituitary cyst (Fig.XVIII.I) which precluded the implantation of any radioactive sources. The immediate post-operative phase was uneventful, but immediately after an air encephalogram done a week later, there was a sudden onset of a meningitis-like syndrome, with rapid development of bitemporal hemianopia and loss of vision on one side. At craniotomy it was found that there had been a large haemorrhage, possibly from a cavernous sinus. After removal of clot, and partial hypophysectomy, there was loss of visual abnormality and a good clinical regression of the acromegalic disease without hormone dependency.

The third case (case S.Cl.) developed bitemporal hemianopia, crossing the vertical meridian, 15 months after an implant of gold-198 planned to give the diaphragma sellae 10,000 rads. A second implant of yttrium-90 was done on the belief that the condition was due to further tumour growth, but led to no improvement. At craniotomy, the chiasma was adherent to the pituitary surface, which had sunk down into the fossa. She had never had clinical meningitis. She had had a course

of 4,000 rads by external irradiation a year before her first implant.

Diabetes insipidus. There were only three operations which were followed by sufficiently severe diabetes insipidus to require pitressin, although there were four other patients who had less severe symptoms. In only one, does this appear to be permanent.

DISCUSSION

Evidently clinical regression of acromegaly can be induced by these needle implants. The regression has frequently been considerable and has included regression of the acromegalic facies, and loss of headache and paraesthesiae. Such regression has been apparent immediately following operation, and has continued to advance over the next few years. In addition to these clinical improvements, there have been regressions of "jaw" size, loss of abnormal insulin resistance, loss of frank diabetes and of biochemical pre-diabetes, and loss of metacarpal cortical thickness. On the other hand, there have been complications, including one death, and some patients have been rendered hormone-dependent.

Parameters of disease activity and the effect of implantation.

Headache was one of the commonest symptoms complained of. It occurred in 65% of cases, which is slightly less than in the 130 cases of Davidoff et al. (1927), and Hamwi et al. (1960), and slightly more than in the 100 cases of Gordon et al. (1962). It had no characteristics specific to acromegaly, in agreement with Hamwi et al. (1960). Relief was invariable, when disease regression was induced by implantation. By contrast, external irradiation had only relieved this symptom in two of seven patients treated. A similar correlation between regression of facies, and substantial loss of headache was noted by Molinatti et al (1962). It would seem likely that disease activity per se, can cause headache in that the patient in the present series with a perfectly normal sella radiologically had severe headache (relieved by implantation), while Gordon et al (1962) had a similar case in whom the absence of tumour was confirmed at craniotomy.

Paraesthesiae, mainly in the fingers, but occasionally in the feet as well, was sometimes the worst complaint of these patients; in one case the severity had led to years of intolerable nocturnal discomfort, and in another to multiple operations for "carpal tunnel syndrome". Relief was often dramatic, after implantation, and where this was not so, re-implantation was effective. There can be little doubt that this is

a reliable index of disease activity, and all cases who had a clear regression of acromegalic facies, also lost this symptom.

Regression of the acromegalic facies was in some cases very striking; those with the most pronounced disfigurement showed the most change. There were two patients with but a minor degree of acromegalic facies; in one with paraesthesiae and marked sweating, the response to implantation could be assessed on this, and in the other, response could only be assessed by the ITTa; in both, there was good evidence of response, but neither changed in appearance. In no case was there disability from tongue enlargement.

Change in hand volumes was disappointing. There were only four patients with a reduction of 50 ml. in both hands. However, many patients had smaller reductions of doubtful significance, and it would seem very likely that such changes can be looked for more usefully after the lapse of several years. Patients' statements about loosening rings appear more sensitive.

Dental measurements have not been serially recorded before in acromegaly. Serial models of both jaws, along with acrylic bites for articulation of the jaw, appear to be a most useful and precise measurement. The greatest change in interdental diameter was between the molars, so this seems to be the best measurement to follow. Both upper and lower "jaw" diameters may undergo reduction when acromegaly remission is achieved by pituitary implantation, but not all patients who had a good disease remission showed interdental regression in the year or so they have been followed. On the other hand, no dental change has been found in patients who failed to show disease remission after implantation. The mechanism of the reduction in interdental diameter is not shown by this study. Shrinkage in the size of the tongue could well allow the right and left teeth to move together a little, or alternatively, primary reduction of jaw width could be occurring. A third alternative, which would seem very unlikely, is that the contraction in jaw width could occur with progressive acromegaly advance, in that as prognathism continued to increase,

the width of the jaw might contract. This possibility can be ruled out by the finding that prognathism actually receded in some cases. Finally, jaw contraction might be a normal ageing phenomenon, but this is said not to occur. In some cases, the axis of the teeth initially sloped outwards, and became more vertical after implant, suggesting tongue shrinkage.

It was one of the objectives of implantation to attempt relief of the disease without incurring hypopituitarism. In the event, all six patients who sustained hypopituitarism after implantation for active acromegaly also obtained a good disease remission. On the other hand, six patients had a good remission without hormone dependency being induced. Thus, hypopituitarism is by no means essential to disease remission; doubt of the exact tumour outline precludes deliberate total destruction with yttrium-90. Those patients who did sustain impairment of pituitary function probably did so as a consequence of pituitary infection in four cases, although in three cases , there was nothing to suggest this, and must be assumed to have had the normal adenohypophyseal remnant close to the radioactive sources.

The augmented insulin tolerance test (ITTa) was developed as a possible test of acromegaly activity (Fraser et al., 1962); using the conventional dose of 0.1u/kg., Hamwi et al., (1960) found normal curves in all of seven active acromegalics. The present analysis includes many of the tests already reported; the further tests fully confirm the claim that insulin "resistance" is a useful index of activity. For instance, out of 17 non-diabetic acromegalics tested before implantation, 16 gave an insulin resistance index above the extreme upper limit of normal (142mg.%) while the remaining patients gave a test result of 135mg.% which is in the "possibly abnormal" range. When these patients went into clinical remission after implantation, the insulin resistance index fell, and continued to fall from the third post-operative month to the twelfth month, and a further fall might still occur with longer follow-up. When patients were re-tested after implantation, those with good clinical remissions obtained normal results (9 out of 9), but there were 3 patients who did not obtain good remissions yet did achieve a normal ITTa. Thus, the test may occasionally be normal in both untreated

acromegaly and in incompletely treated patients, so although abnormal insulin resistance characterises the majority of untreated acromegalics, the achievement of a normal test is but a minimum criterion of adequate pituitary suppression by implantation.

Although the detection of "idiopathic" pre-diabetes was the aim in developing the PGT (Joplin et al., 1961), a possible application in gauging the activity of acromegaly was envisaged. In the event it was found that out of 9 acromegalics with normal oral GTTs who were tested before implantation, 6 showed an abnormal PGT. Further, when patients went into clinical remission after implantation, the test abnormality was rectified in all of six such cases. On the other hand, three patients with but partial or no clinical remission of their disease, also obtained normal tests. Hence this test is like the ITTa, in that although most untreated patients have abnormal results, the achievement of a normal test after implantation is but a minimum criterion of an adequate operation. In contrast, improvement in "prediabetic" oral GTT results did not occur after irradiation or surgery in six cases in the series of Hamwi et al. (1960).

Loss of frank diabetes after implantation has occurred in three patients, all of whom obtained striking clinical remissions of the acromegaly. The fourth diabetic patient (case A.Wy.) remained unimproved owing to an ineffective implant (due to a large pituitary cyst). In this series, loss of diabetes has invariably occurred when the acromegaly went into remission, but it would be expected that some patients would remain diabetic even after successful treatment, if they happened to be suffering from what was really "idiopathic" diabetes, or if the growth hormone excess had been present for a long time, and had led to irreversible islet cell damage. Such an example was quoted by Molinatti and his colleagues (1962). Such metahypophyseal diabetes has been shown by Professor F.Young (1961) to occur after repeated growth hormone administration in adult cats and dogs. It is of considerable interest that he found that these animals became insensitive to insulin before the blood sugar began to rise. This short phase may well be similar to the insulin "resistance" shown by the ITTa in non-diabetic acromegalics. Professor Young found

increased plasma insulin-like activity in these as yet non-diabetic animals, as indeed was found in some acromegalic humans by Randle (1954). He therefore thought that the insensitivity to injected insulin might have been due to the injected dose being but a relatively small addition to an abnormally high level of endogenous insulin. Raised plasma insulin has been found subsequently by a number of workers, in acromegaly (e.g. Karam et al., 1963).

Regression of skeletal overgrowth has not been hitherto recorded after treatment of acromegaly. Although measurements on radiographs are best made by densitometry, changes were readily seen in some of the patients by simple inspection of radiographs of the hands. In eight patients whose disease response was assessed on other grounds, serial radiographs were available for inspection for 2 to 3 years after implantation. It was found that in 4 of these patients, there was a measureable reduction in thickness of the metacarpal cortex, without reduction of the diameter of the shaft. Clinical and other test criteria showed marked improvement in these 4 patients' disease. However, 4 other patients who also showed good disease remissions had no such bone regression yet. It would therefore appear that the occurrence of obvious bone thinning is a good sign of disease response, but failure of such bone regression to occur does not preclude an otherwise good result.

The abnormalities in calcium metabolism have not been fully assessed in this series yet. There was no instance of a raised serum calcium or alkaline phosphatase in the 21 patients studied before implantation, and there was but an isolated case with a high serum inorganic phosphate. It is often stated that a high serum phosphate is not infrequently found in untreated acromegaly (e.g.Soffer, 1956), and that a reduction offers good evidence of successful treatment (e.g.Kinsell et al., 1948; Hamwi et al.,1960). However, the number of studies relating serum phosphate to objective estimates of disease activity are few. Quite wide sporadic variation in the serum level was noted by Hamwi et al. (1960). Molinatti et al., (1962) found but four patients with slightly raised values out of 16 studied; the level in all four

fell to normal after otherwise effective treatment by Y-90 implantation. Also, Lawrence and his colleagues (1962) found that an elevated serum phosphorus fell to normal after heavy particle therapy in 9 out of 12 cases; many of these patients had striking clinical remissions. The serum calcium has generally been found to be normal in acromegaly, although Molinatti et al. (1962) found four patients out of 16 with slight elevations. Again there was a fall to normal after implantation. Hyperparathyroidism from parathyroid hyperplasia may be associated with acromegaly (Gordon et al., 1962).

Hypercalcuria was quite common in the present series. Fifteen patients were tested on a low calcium diet, and seven had a urinary loss exceeding 15 mEq./24hours. Change after implantation has not yet been adequately followed in this series, but Molinatti and colleagues (1962) found the urinary calcium to exceed 15 mEq./24hours in 11 of 14 untreated acromegalics; 5 out of 6 followed up for over six months reverted to normal following pituitary implantation and all showed improvement in the acromegalic facies. It would thus appear that loss of hypercalcuria is a good sign of disease remission, and this might well be anticipated from the well known fact that growth hormone can induce a rise in urinary calcium without hypercalcaemia (Medical Research Council Panel, 1959). The mechanism of the hypercalcuria is yet to be fully explained. Perhaps the finding of Karam and colleagues (1961) that growth hormone given to hypophysectomised rats causes a fall in renal citrate along with the hypercalcuria, is relevant. Other contributory factors may be increased absorption of calcium from the small gut under the influence of growth hormone, shown in rats (Finkelstein and Schachter,1962) and man (Henneman et al.,1960). Kinetic analysis of intravenously administered calcium-47 to one of the patients in the present series before implantation showed a slightly low index of bone accretion, and a very low index of bone resorption (to be published). Further studies of thie type, as well as absorption tests, may throw further light on the paradoxical coexistance of osteoporosis and new bone formation and hypercalcuria of this disease.

One of the objectives of all types of treatment of acromegaly is

to prevent further tumour growth. In the present series, there was no instance of fossa expansion shown radiologically after implantation, while the period of study has thus far covered 34 "patient years". Before the effect on tumour growth can be fully assessed, however, many years must pass, as signs of tumour re-growth after surgery may not be manifest for decades (Henderson, 1939). However, Arner and his colleagues (1958) reviewed 16 acromegalics who had been treated by external irradiation 2 to 26 years previously, and found that but one of these patients had had further expansion of the sella.

The present series of acromegalics, whose diagnosis was confirmed not only by various objective tests, but also (in most) by the clinical regression of disease after implantation allows an opportunity to investigate in detail the radiological features of the pituitary fossa in this disease. In 20 patients, the radiographs were specially examined (Table XVIII.II). The important findings were that only one patient had a pituitary fossa which appeared entirely normal on the plain lateral radiograph. The commonest abnormal measurement was an increase in area of the fossa, even when the smallest visible contour present was used for delineating the area (The upper limit of normal for this measurement, (see Chapter III) as made directly on the x-ray is 145 sq.mm.) There was only the one patient out of the 20 in whom the fossa was both of normal area, and showed no second contour. Thus, this is the only patient in whom there might be any value in introducing a measurement of volume to assess fossa normality. In the event, the width of the fossa in this patient was well within the normal range, so the volume also would be perfectly normal. The present series therefore gives an incidence of 95% of acromegalics with an enlarged pituitary fossa, which is similar to the report of Davidoff in 1926, who found an enlarged fossa in 93 of his 100 acromegalics; 25 out of 30 cases had definite enlargement of the sella in the series of Hamwi et al (1960), and 76 out of the 100 cases of Gordon et al. (1962).

Other classical signs of pituitary tumour, such as undercutting of the anterior clinoids (implying that the tumour is fairly wide),

thinning of the dorsum sellae, and erosion of the posterior clinoids were found in a minority of patients. In general, the findings were similar to those of Mahmoud (1958) in a study of radiographs of 49 pituitary adenomata.

Complications of implantation

Complications from the present series were mainly related to infection within the tumour. Infection was probably more common (7 out of 24 operations) in patients treated with gold-198 with or without Y-90, when the peak dose to the diaphragma sellae was only 10,000 rads, than when a high dose of Y-90 was used so as to give the diaphragma sellae about 100,000 rads (1 infection out of 8 operations). This may well be due to the greater sterilising effect of the more active seeds. Molinatti et al. (1962) reported no cases of infection in 16 implants, using 2 to 5 pellets of yttrium-90 of very high activity (4 to 10 mc each). They had but one instance of C.S.F. rhinorrhoea, and 3 of cranial nerve damage (which were largely temporary). Fortunately if such infection is recognised early and treated with antibiotics, even if the C.S.F. appears normal, clinical response is quite rapid. Chloramphenicol appears to be particularly effective, and it would appear wise to initiate treatment using this antibiotic, and after about two weeks, to replace it with a less toxic antibiotic which can be taken orally, such as tetracycline, and continue this for a further 3 months to reduce the risk of recurrence.

C.S.F. rhinorrhoea occurred occasionally (4 in 32 operations), and in 2 cases, treatment with a screw insertion was required. In one, this was unsuccessful, owing to the anterior fossa wall being very thin, and so surgical repair was needed. External irradiation may also be followed by C.S.F. leakage, necessitating surgical repair (Gordon et al., 1962). Late chiasmal damage was sustained in two cases. In both this was due to the subsidence of a large tumour leaving a large cavity into which the chiasma was forced (or dragged, due to adherence to the tumour). Presumably, this would be a risk arising from any operation which caused tumour contraction. There was an isolated instance of haemorrhage in the pituitary area. A very large cyst had precluded implantation, but

an ill-timed air encephalogram done a week post-operatively was immediately followed by bilateral visual loss, necessitating clot removal neurosurgically. There was no clinical evidence of oculomotor nerve damage.

The results obtained in the present series can now be compared with reports in the literature, of radiotherapy, surgery (alone, or combined with radiotherapy), hormones and pituitary implantation.

Results of external irradiation.

External roentgen irradiation has undoubtedly given periods of benefit to many reported cases. Benefit was claimed in 59 out of the 93 cases in the series of Vaughan (1938), Ellis (1949), Johnsen (1952), and Hamwi et al., (1960). Despite the conventional view that optic nerve pressure is an absolute indication for surgery, it was found from the literature that after external irradiation of 58 patients with visual field defects, improvement in the visual fields followed in 29; there was no change in 17, and a deterioration occurred in 12 (Jusefowa et al., 1930; Dyke and Hare, 1938; Kerr, 1948; Hurxthal and Younghusband, 1949; Johnsen, 1952, Arner et al., 1958 and Hamwi et al., 1960). Recently, Colby and Kearns (1962) reported on 22 acromegalics with visual loss treated by external irradiation; 10 showed either improvement or no change in vision when assessed after three years. Regression in soft tissue overgrowth was rarely observed, though when the aim has been to give repeated courses until either regression occurs, or a cumulative dose of 8,000 rads has been given (Johnsen 1952), some impressive regressions occurred (13 out of 19). Single courses of up to 4,000 to 5,000 rads preferably administered within 3 weeks, usually gave several months' relief from paraesthesiae and headaches, but rarely regression in the acromegalic overgrowth. This appears to be the limit of tolerance of the optic chiasma for a single course, (e.g.Lindgren, 1958), while damage is liable when cumulative doses reach 10,000 rads (Kelly et al.,1951; Buys and Kerns, 1957). If there is no improvement after an initial course, it seems safe and effective to repeat the course after three months.

External roentgen irradiation in doses up to the limits of safety had been given to eight patients in the present series, yet without a single instance of regression of overgrowth or other objective sign of improvement, and there was no prolonged remission of paraesthesiae, but two had improvement in headache.

External irradiation of the pituitary by high-energy heavy particles seems to offer an entirely new approach. Here, advantage is taken of the great power of penetration and relatively low scatter in tissue of 900 MeV alpha particles. The beam is produced by a synchrocyclotron and concentrated on the pituitary by head rotation. The results of treatment of 17 patients with acromegaly have been reported by Lawrence's group (1962) in Berkeley. The pituitary dose was 4,000 to 9,000 rads given in 11 to 21 days. Most of the patients had striking disease remission; for example, 5 of 15 showed regression of the acromegalic facies, 9 of 12 had reduction of elevated serum phosphorus to normal. Three patients subsequently required cortisone or thyroxine. Three patients who initially had normal vision showed subsequent impairment. There were no other complications. From this report, there is no doubt that this is a promising type of treatment, and might be further improved if the Bragg peak properties of heavy particle beams could be exploited by even more accurate localisation.

Results of surgery.

Surgical treatment of acromegaly has on the whole been disappointing until more recent series have been done attempting a more radical excision. Henderson (1939) reported on a large series of cases treated surgically by Cushing. Most had had a transphenoidal operation. Field defects improved in 11 out of 12, but in a follow-up of 5 to 23 years, 20 out of 59 patients had died of recurrence of the disease, 7 due to intracranial extensions. The mortality due to treatment was 8.6%. From this series, and Bakay's (1950) report on Olivecrona's series, it appears that striking regression of the disease has been unusual. Hirsch (1959) however, claimed good regressions in 9 acromegalics treated by a trans-sphenoidal operation, quoting a final mortality rate of 2%. Higher

surgical mortality of 16.4% with tumour surgery was quoted by Decker and Lauter (1960), and even higher figures were quoted from reviewed series. Hamberger and colleagues (1959) using a transantrosphenoidal approach and total hypophysectomy in 10 cases reported that all signs of pituitary overactivity had disappeared and soft-tissue manifestations showed significant regression, yet without mortality or serious morbidity; panhypopituitarism occurred in four. Ray (1960) did 12 surgical hypophysectomies for acromegaly, with but one (possibly unrelated) post-operative death; 11 were said to have had "some measure of benefit". These later series have included many cases treated for the endocrine abnormality per se.

Combined surgery and external irradiation appears to have advantages in reducing the incidence of recurrence (Grant, 1939; Henderson 1939). Prior irradiation is said not to preclude surgery (Grant 1939).

Although Kirklin and Wilder (1936) reported regressions with oestrogens in small doses, there is a lack of subsequent reports of striking results. More recently, Kinsell and his colleagues (1948) also noted a fall in serum phosphorus from androgen and oestrogen treatment.

Plan of implant.

The question of the ideal radioactive dose to be administered in the implantation treatment of acromegaly is still to be finally answered. It is clear from the present series that regressions can be obtained with Au-198 sources giving only 10,000 rads at the estimated gland surface, but in many cases, this is an inadequate dose. At the other extreme, all patients in the present series re-implanted with Y-90 giving a dose of 100,000 rads at the gland surface obtained excellent results, yet without chiasmal damage, or inevitable hypopituitarism. At the present, a series is being done using a combination of Au-198 and Y-90, aiming to give a dose at the estimated gland surface of 5,000 rads from each source (10,000 rads peak dose). Molinatti et al. (1962) used 2 to 5 pellets of Y-90 whose individual activities were 4 to 10 mC. Their pellets being 1.3mm. diameter and 4 mm. in length would be comparable to the 4 mm. rods used in the present study. Hence, their 4 mC pellet

would deliver about 100,000 rads at 5 mm., and their 10mC pellet 100,000 rads at 6 mm. Thus, the dose at the gland periphery in their 2 patients with a radiologically normal sella would be about 300,000 rads, while in a patient with a really large sella, it could be very small. Yet 13 of their 16 patients had improvement in acromegalic features and the field defects showed total disappearance in the two affected patients. It would appear that a massive central dose is highly effective in relieving acromegaly, yet it only led to adrenal insufficiency in one case out of 16. Perhaps the results of the present series would be improved by increasing the planned dose to the diaphragma sella from Y-90 to about 20,000 rads - a dose which would probably not lead to total pituitary destruction, yet would cause the major part of the tumour to undergo necrosis. While this dose could not be achieved at the surface of a large tumour, at least the central part of the tumour would be totally destroyed.

The ultimate criterion of success in the treatment of acromegaly is a lessening of the hazards known to beset these patients if untreated. The seriousness of acromegaly may well be generally underestimated, owing to the rarity of the condition, and slow evolution of its complications. A significant finding of Bishop and Briggs (1958) was that 80% of a group of about 100 acromegalics had died before the age of 60, and they concluded that "the modern treatment of acromegaly is not sufficiently radical".

SUMMARY AND CONCLUSIONS

1. 15 patients treated by the implantation of Au-198 seeds, planned to give a dose of 10,000 rads at the normal radiological level of the diaphragma sellae, were fully assessed post-operatively. Entirely satisfactory results (facies regression, loss of symptoms, and a normal ITTa and PGT) were obtained in 5, partial response in 5, and no improvement in 5.

2. Re-implantation was done in 8 patients, of whom 7 obtained a satisfactory disease remission. In 4 the dose plan was to give the diaphragma sellae 100,000 rads from Y-90 alone, in one it was 10,000 rads from Y-90 alone, and in 2 it was 10,000 rads total from Y-90 and Au-198. A single re-implant was done with a planned dose to the diaphragma sellae of only 1,000 rads from Y-90 alone, and it was without any effect.

3. Of a total initial group of 16 patients whose response has been fully assessed, 12 are now in satisfactory remission.

4. Using plaster models, serial measurements showed a reduction of interdental diameters (in both jaws), and prognathism in 4 of 7 patients undergoing good clinical remissions. No change occurred in 2 patients showing no general disease response. Measurements made clinically with a caliper were in agreement with the models.

5. The ITTa showed insulin resistance of an abnormal extent in 16 of 17 non-diabetic patients before implantation, and there was a borderline result in the exception. Following a clinically satisfactory operation, the test invariably showed normal results, but also gave normal results in 3 patients with but partial or no clinical regression. The insulin resistance index continued to fall in all of 6 patients who were tested both at 3-6 months and again at 12-30 months.

6. The PGT was abnormal before implantation in 6 of 9 acromegalics with a normal oral GTT. After operation, all of 6 with satisfactory

clinical remissions had a normal test, but 3 with but partial clinical responses also obtained a normal test result.

7. Four of the acromegalics treated had clinical diabetes mellitus. Three obtained a normal GTT after operation, and 2 of these also had a normal PGT. The fourth patient not only showed no amelioration of diabetes, but showed no other evidence of disease response.

8. Serial x-rays of the metacarpals in 8 patients who had satisfactory disease remissions on other criteria showed a conspicuous reduction in the thickness of the metacarpal cortex in 4; it was first visible at 18 months.

9. Serial x-rays of the pituitary fossa were taken in 13 patients for over one year after implantation. No further enlargement occurred in any, in a total of 34 "patient-years".

10. Complications of the procedure were largely due to infection of the tumour, and comprised a meningitis-like syndrome (8 out of 32 operations) usually with a sterile C.S.F. Response to antibiotics, especially chloramphenicol was usually prompt, but recurrence was liable unless some antibiotic cover was maintained for three months. There was one death due to undiagnoeed pituitary abscess and hypopituitarism, and another patient sustained recurrent bouts of meningitis. Chiasmatic defects occurred in two patients as a result of shrinkage of the tumour which carried downwards the adherent chiasma. A C.S.F. leak occurred after four operations. It soon ceased in two cases, was successfully arrested by the insertion of a screw in the third, and required surgical repair in the fourth.

11. Replacement therapy with cortisone and thyroxine was required in 7 of the assessed patients. All had obtained excellent disease remissions.

12. The ideal irradiation dose was shown to be greater than 10,000 rads at the tumour periphery, when given by Au-198 alone. It is suggested that 20,000 rads, given by Y-90 alone, would be safer and more effective.

APPENDIX I.

In this appendix will be found detailed case reports of two patients. One had disseminated breast cancer, and one had acromegaly. These two patients have been selected to illustrate features of disease remission, and also to show the type of serial observations that have been made on most patients with these disorders.

Case report on a patient with disseminated breast cancer (Case O. Wi.).

In 1953, at the age of 31 years, a radical mastectomy was done when a small lump was noticed in the left breast. At radical mastectomy, a scirrhous carcinoma was found, and the axillary nodes were involved. Deep x-ray therapy was given. A year later, there was local recurrence in the scar, and backache and weakness of the right leg. X-rays showed osteolytic metastases in the spine and pelvis. In 1955, bilateral oophorectomy was done, and this immediately relieved the back pain and halted the advance in the skeletal deposits. This was a striking clinical remission and it lasted for two years.

In May 1957, a lump appeared in the other breast, and was removed by simple mastectomy. It was histologically identical to the first. At the same time, there was recurrence of backache, which rapidly became very severe, so that even moving in bed was extremely painful. X-rays showed numerous new metastases in the vertebrae, skull, and ribs. There was no pain relief, nor radiological improvement, from oral methyl testosterone 40mg./day. A sensory level at D.8 appeared, and both legs became weak. There was absent vibration and joint sense in the feet, with partial analgesia. The serum calcium was 5.6 mEq./l, urine calcium 17 mEq./day and alkaline phosphatase was 25 K.A. units/100ml. The pelvis x-ray is in Fig.A.3 (2/10/57), and clinical photo in Fig.A.4. November 1957: Transfrontal insertion of 9 seeds of Y-90 by Mr.G.C.Knight. This led to immediate pain relief and loss of the sensory level at D.8., but no other neurological improvement. The serum and urinary calcium fell to normal but the alkaline phosphatase did not rise. The implant-

ation had not caused demonstrable hypopituitarism, in that the patient was not clinically steroid dependent, had three normal water diuresis tests (90%, 99% and 104%), the urinary 17-KGS was 23 and 20mg./24hrs., and there was a normal I-131 uptake of 27% at 48 hours. Unfortunately, she developed diabetes insipidus on the fourth post-operative day, and required pitressin tannate injections for the next four months.

On the 13th post-operative day, the vision in the right eye became blurred, and a right upper nasal quadrantic field loss was found. By the 26th day there was a total right upper hemianopia, with severe visual loss (Jaeger 16). These never improved and optic atrophy appeared. The delayed onset of the lesion is quite typical of irradiation damage, and x-rays taken five days after operation showed that although eight seeds had been safely placed within the pituitary, there was one seed situated at the level of the diaphragma sellae, and situated as far laterally as the right edge of the pituitary gland, and just posterior to the tuberculum sellae. This seed could have been almost in contact with the undersurface of the right optic nerve. The seeds were of such an activity that a dose of 100,000 rads would be given at a point 3 mm. distant. The average thickness of the optic nerve is about 3 mm., so it is probable that as damage was sustained to a little more than half the thickness, and the irradiation dose tolerated before histological defect is apparent in monkeys is 56,000 to 130,000 rads (Rasmussen, 1953), it is probable that the seed was situated 1 to 2 mm. from the nerve surface. Tracings of the post-operative x-rays are shown in Fig.A.1.

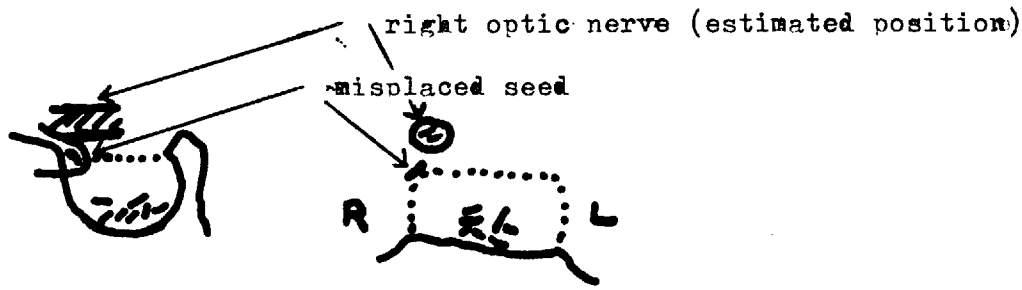


Fig. A.1. Tracings of lateral and antero-posterior x-rays showing the position of the Y-90 seeds after the first (transfrontal) implantation. Severe irradiation damage was sustained by the right optic nerve.

The clinical remission lasted for 3 months and she was able to walk a little with two sticks. Then the bone pain returned, with such severity that she became totally bed-ridden. At this stage, the serum and urinary calcium became very high, a leukoerythroblastic anaemia appeared, and skeletal x-rays showed an increase (Fig. A.3, 8/4/58) in metastases. In view of the temporary but definite remission induced by incomplete pituitary ablation, a second implantation was planned.

April 1958: Transnasal needle implantation of 8 Y-90 seeds. Following this operation, there was once again a dramatic loss of bone pain, and improvement in well-being. The serum and urinary calcium fell to normal and there was a brisk but temporary rise in serum alkaline phosphatase. The anaemia, which initially required regular blood transfusions, finally resolved, and nucleated red cells and primitive white cells vanished from the peripheral circulation. These changes are shown in Fig. A.2. Unfortunately, during a fit on the 5th post-operative day, she sustained a pathological fracture of the right femur. This healed so that she was discharged walking in a caliper in September 1958, and all the other skeletal deposits showed massive calcification (Fig.A.3). The vibration sense remained absent in both legs, but the weakness in the left leg greatly improved.

Unfortunately, she was still not steroid dependent, with a WDT of 112%, and 17-KGS at the time of the stress of the femoral fracture was 9 and 7 mg./24hrs. The I-131 uptake was 42% and later 39%, no signs of subthyroidism developed in 8 months, and the urinary FSH was over 12 m.u./24hrs.

She remained very well for a total of 6 months, until vomiting began, along with profound weakness, and recurrence of bone pain. At this time, the serum calcium and urine calcium were again rising, and the blood urea rose to 85mg%. New skeletal metastases were appearing and the haemoglobin had fallen to 43%. Accordingly, arrangements were made for a third attempt to ablate the pituitary.

December 1958: Transnasal implantation of Y-90 seeds. Following this operation she rapidly recovered robust health and lost the bone pain.

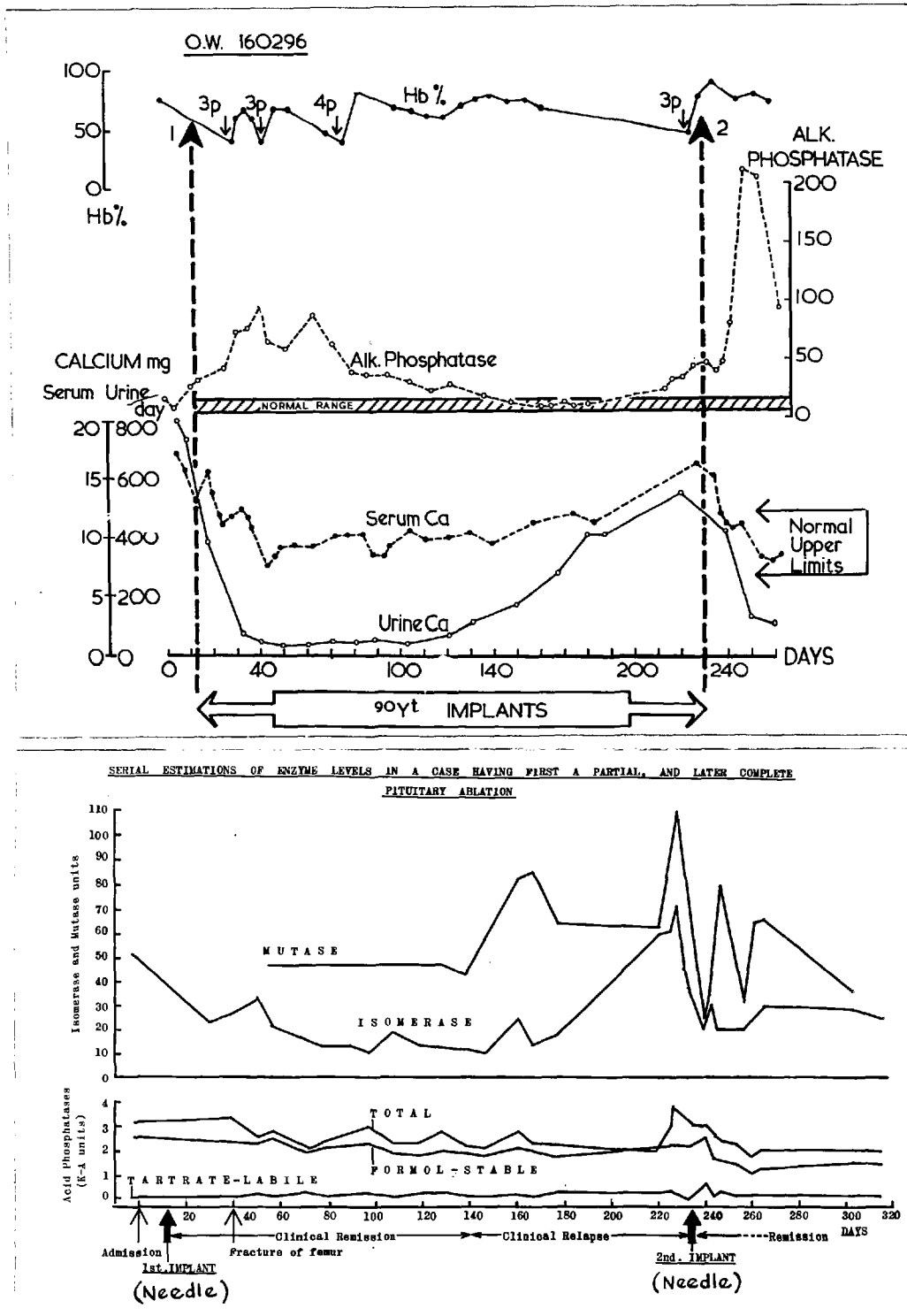


Fig. A.2. These serial observations were made over the period which commenced just before the second Y-90 implant (shown as first needle implant in lower figure) and continued 4 weeks after the last implant. Blood transfusions are shown as 'P' (pints) in the upper graph.

The vomiting ceased, and a few months later, she was back at work in a responsible position. She took a travel holiday unaccompanied. A clinical photograph is reproduced in Fig. A.4 (b). The serum and urinary calcium and blood urea all rapidly fell to normal, and a brisk but temporary rise in serum alkaline phosphatase occurred. The skeletal deposits were clearly calcifying in x-rays taken 10 weeks post-operatively, and remodelling of trabeculae in these area continued to occur in serial x-rays (Fig. A.3) up to her death.

This time, pituitary ablation seemed complete. She was clinically steroid dependent, showing steroid withdrawal symptoms 5 days after the last dose of cortisone had been given, and a concurrent WDT was 46%. There was an immediate clinical improvement on re-instituting cortisone, and restoration of the WDT to 97% after 48 hours. By 3 months there was clinical myxoedema, with a serum cholesterol of 405 mg.%, and the I-131 uptake was a little higher than is usual in this context, being 23%. Thyroxine was begun.

She remained fully employed and in complete cancer remission, subjectively and objectively, up to the terminal illness which consisted of repeated epistaxes. Surgical exploration showed the bleeding to be coming from the pituitary fossa, and was too brisk to be arrested. She died in January 1961, just over 3 years after the first (transcranial) implant. At autopsy, it was found that the haemorrhage was coming from a perforation in the right anterior carotid artery in the anterior part of the cavernous sinus. This would be closely related to the position of the seed which had been responsible for the right sided hemianopia following the first (transcranial) implant.

Comment

This is a very important case, as it illustrates the principle that a breast cancer which is sufficiently hormone dependent to show a really striking and prolonged remission after complete pituitary ablation, may also show a remission to but partial ablation. However, the duration of the remission from partial ablation is very much less impressive and shorter than can be obtained with total ablation.

This feature was demonstrated on two occasions in this patient; shs had two incomplete pituitary ablations, yet after each there was a definite clinical and radiological and biochemical remission lasting a few months on each occasion.

It was particularly fortunate that it was possible to obtain serial observations on the serum and urinary calcium, serum alkaline phosphatase, blood picture, and bone metastases. In this way, the close agreement between all these parameters and clinical response could be assessed, and in fact, all were found to agree perfectly. The fall in serum and urine calcium, and the rise in serum alkaline phosphatase, all begun a week after implantation, thus providing evidence of remission a long time before there was any radiological skeletal recalcification.

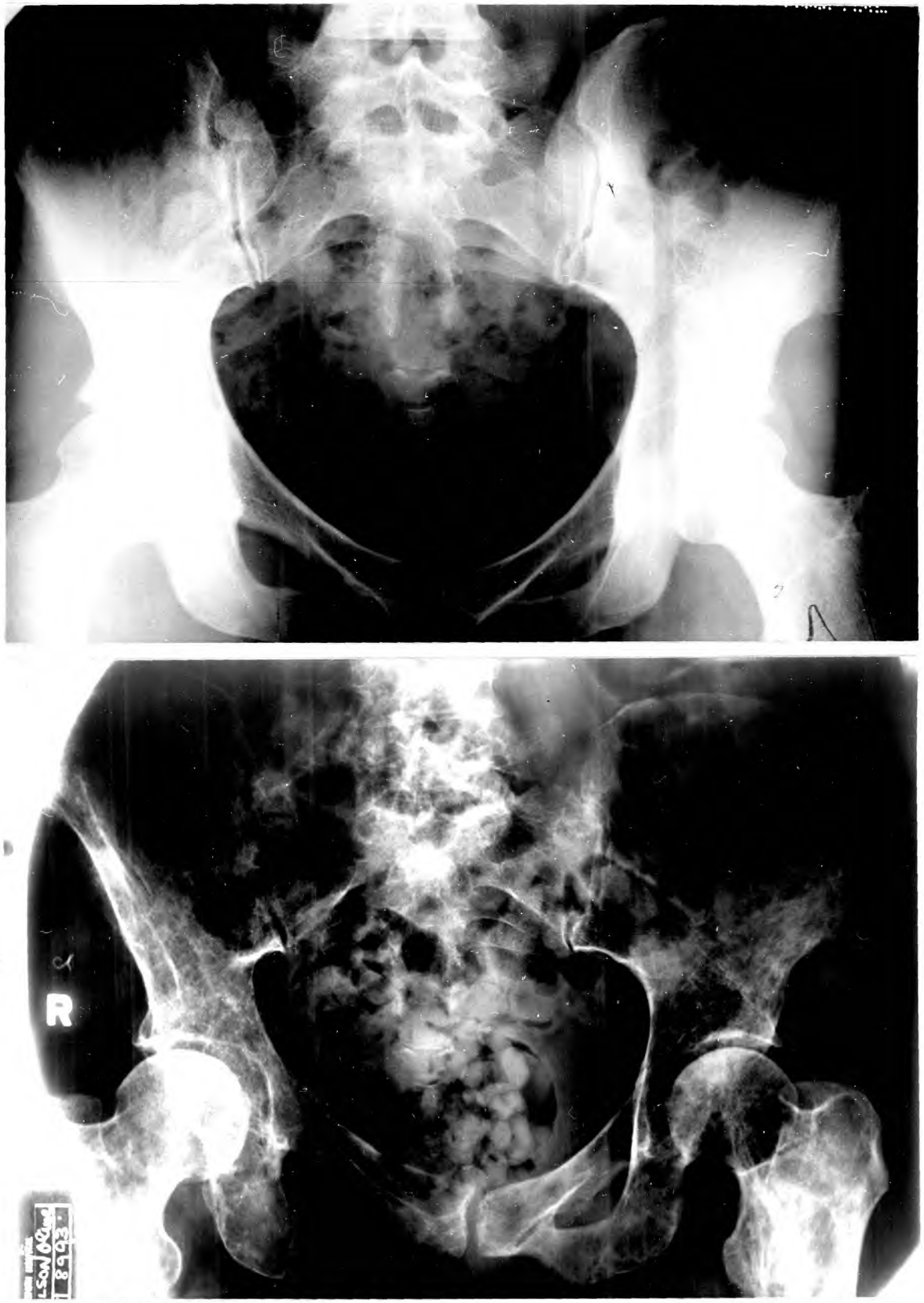
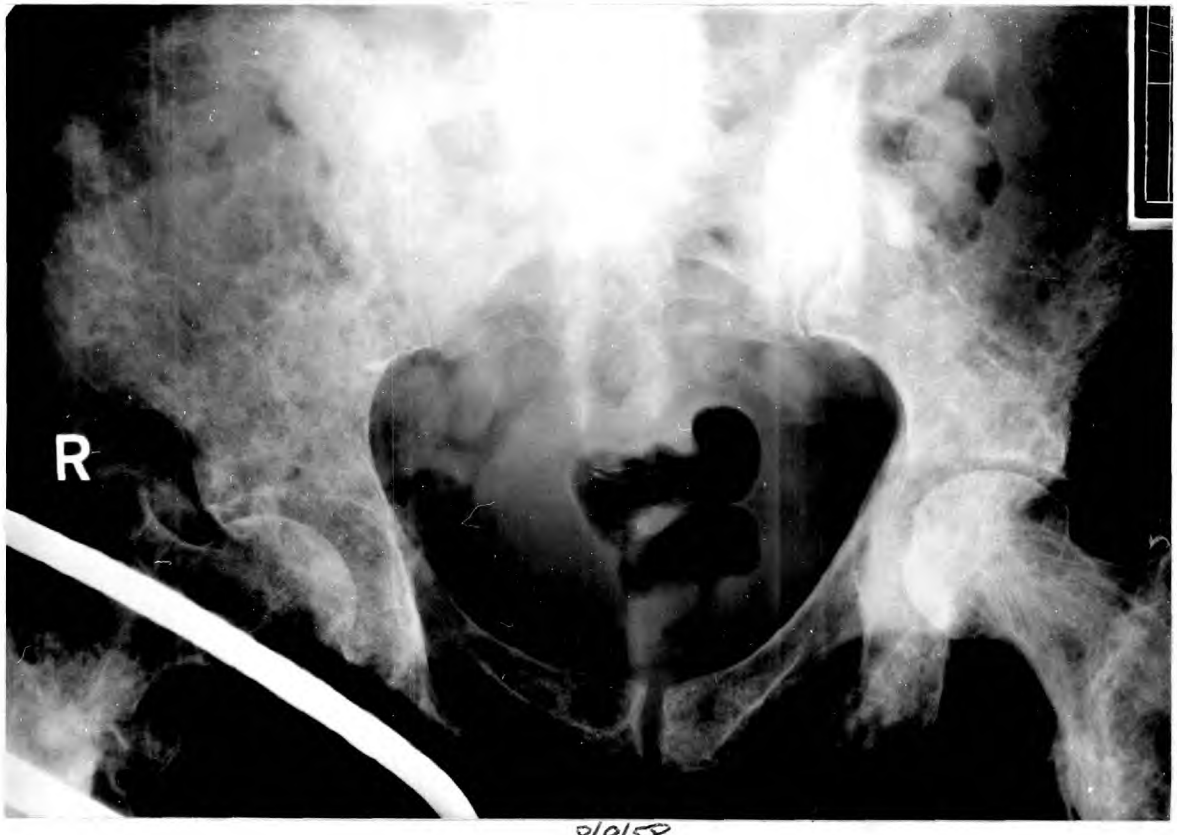


Fig. A.3. Serial pelvis x-rays.



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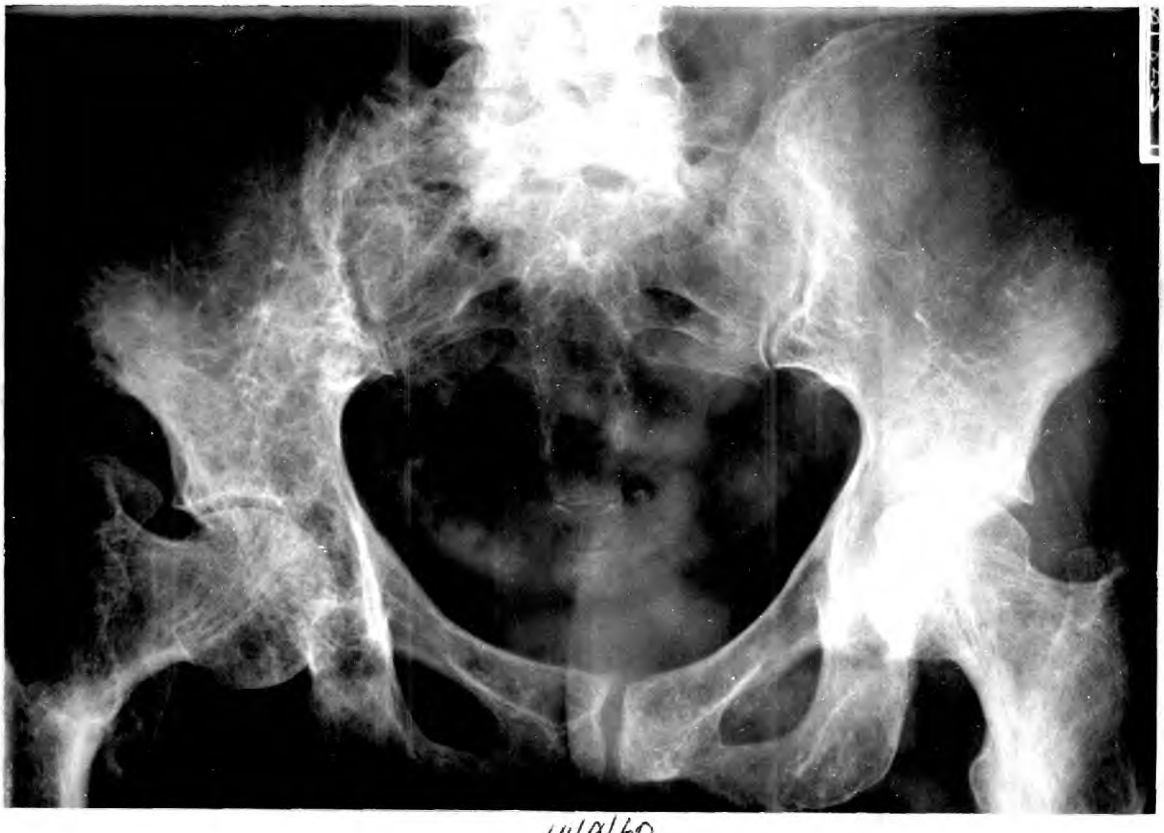

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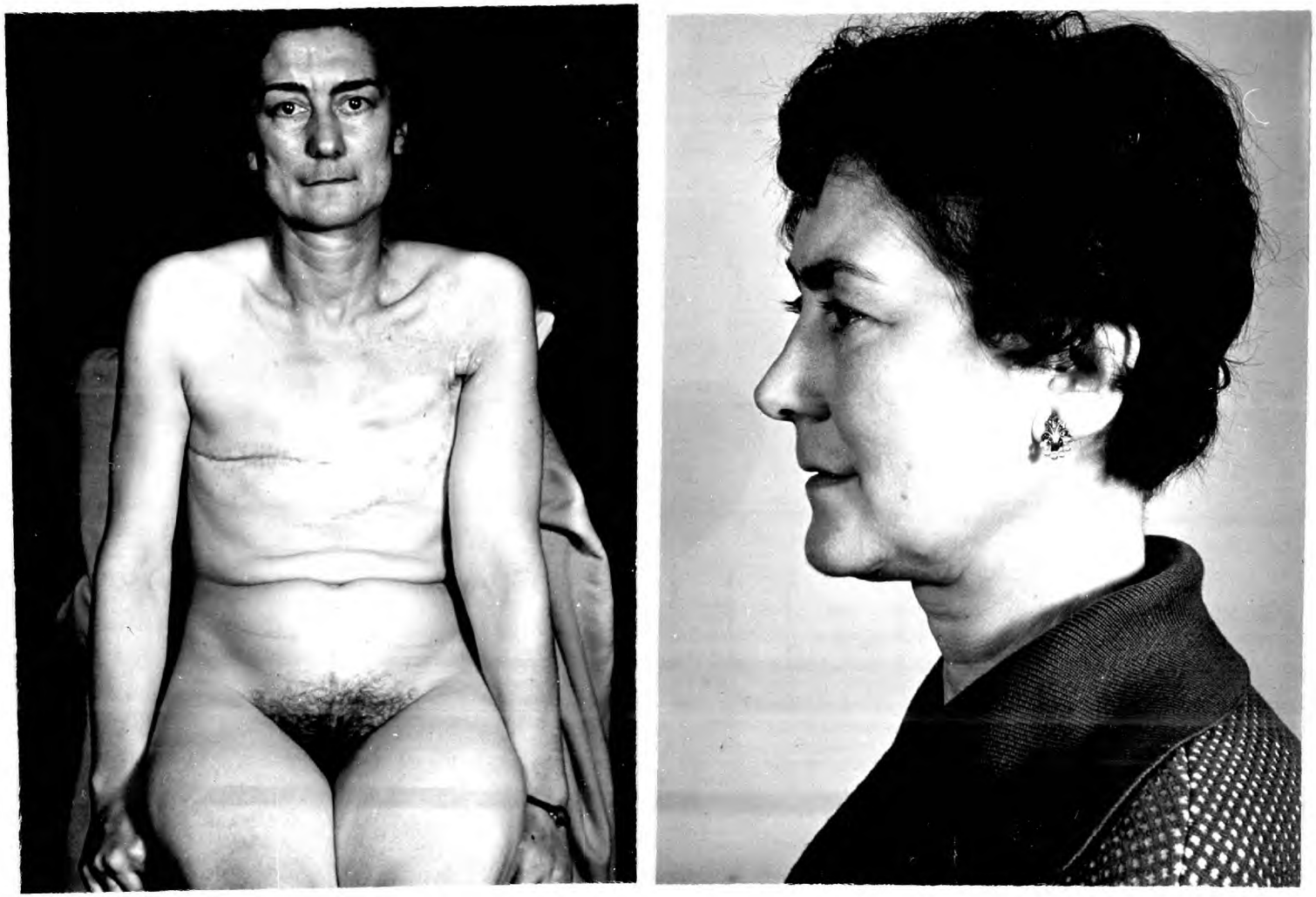

Fig. A.4. Case O. Wi. (a) 19/11/57 before transcranial implant (b) 26/3/60, in full remission

Case report on a patient with acromegaly (Case S.Ri.).

This man was first seen elsewhere in 1956, when the diagnosis of acromegaly was made. He had had headache since 1950, and recent onset of enlarging hands and feet and coarsening features.

Treatment had been given in January 1959 by a course of external irridation, totalling 3,500 r., from a linear accelerator, but this had no effect on any of the above features. He then developed diabetes mellitus.

He was first seen personally in August 1959 at the age of 40, complaining of mild headache. There were no paraesthesiae. He was noted to be markedly acromegalic (Fig.A.6), moderately hirsute, and had a conspicuously large tongue. The skin was abnormally thick and greasy. He was edentulous. The thyroid was impalpable, and he appeared clinically euthyroid. The B.M.R. was normal (+9% on two occasions), and so was an I-131 test. The hand volumes were 653 and 605 ml. He had mild diabetes, with a fasting blood sugar varying between 92 and 157 mg.%, and a frankly diabetic glucose tolerance test. Skeletal x-rays showed marked thickening of the metacarpals and phalanges, and thickening of other bones. The serum calcium was 5.1 mEq./l., inorganic phosphate 2.2mEq./l, and serum alkaline phosphatase 10 K.A. units/100ml. On a calcium intake of 0.3 mEq./kg. body weight, the urinary calcium was 28 mEq./day, (very high) and he was in negative calcium balance of 15 mEq./day.

X-rays of the pituitary fossa (Fig A.5) showed a moderate general enlargement, the actual measurements on the films being as follows: area, 207 sq.mm. (normal <145 sq.mm.); depth 15 mm. (normal< 14 mm.); length 18 mm. (normal < 17 mm.). A double contour was visible, but the two contours were not markedly different. There was no thinning of the dorsum sellae. The fossa floor was clearly seen in the straight antero-posterior projection. It was concave upwards, the concavity being symmetrical, and maximum at the mid-line. This was confirmed by lateral tomograms. An air encephalogram failed to show the area immediately above the pituitary; this would be consistsnt with a suprasellar extension. Tests of pituitary function in addition to the above finding

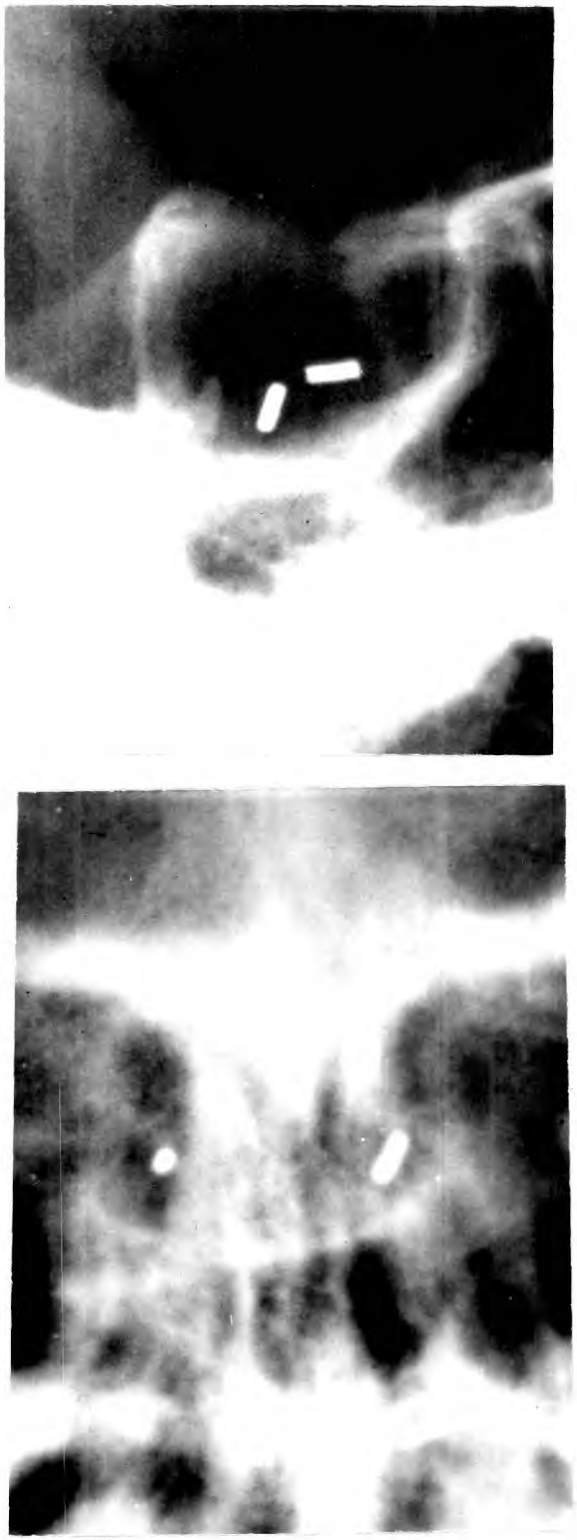

Fig. A.5. Lateral and antero-posterior radiographs showing the two Au-198 seeds.

of normal thyroid function, were urinary FSH greater than 96 m.u./24hrs., 17-KS 15 mg./24hrs., and 17-KGS 7 mg./24hrs. Response to Metopyrone was normal, the 17-KGS rising threefold to 25 mg./24hrs. The visual fields and optic fundi were normal. Acuity was slightly impaired in one eye, in connection with a slight strabismus.

October 1959: Needle implantation of two seeds of Au-198 (Fig.A.5.)

The implant plan was to deliver 10,000 rads to the gland surface. The seeds were 13.3mC each. Post-implant radiographs showed that the peak dose to the diaphragma sellae, assuming it to be in the usual position, was 8,000 rads, and approximately 60% of the gland received over 10,000 rads.

The immediate post-operative course was rather stormy, in that on the second day he developed a severe headache, stiff neck, and temperature of 100.5°. The C.S.F. was clear, sterile, and contained 10 white cells/ c.mm., and the protein was 150mg.%. The meningitis-like syndrome soon settled on antibiotics which were withdrawn after a month. There was no recurrence. It is assumed that he had sustained an intra-pituitary abscess. There was mild diabetes insipidus for a few weeks, but pitressin was not needed.

Three months after implantation he was reassessed. He had had no cortisone or thyroxine. He was clinically found to be rather lethargic, but he had lost his headaches, and sweating was now normal. Tests of adrenal function showed some impairment. The WDT was 14%, 17-KGS was 1 mg./24hrs., and there was no rise with Metopyrone. The I-131 test was entirely normal (uptake and "T" index), and the cholesterol was 168 mg.%. The acromegalic facies had shown a marked regression, and he was less hirsute. He was no longer diabetic, and a prednisone glycosuria test for pre-diabetes was also normal. An augmented insulin tolerance test showed an index (the sum of the 60, 90 and 120 minute blood sugars) of 68, which is perfectly normal. This test is shown in Fig. A.7 and compared with the normal range (hatched), and the pre-implant test. Actually, the pre-implant test cannot be fairly interpreted, as it commenced with a raised fasting level. The urinary calcium and calcium balance were re-checked on the same calcium intake as pre-implant.

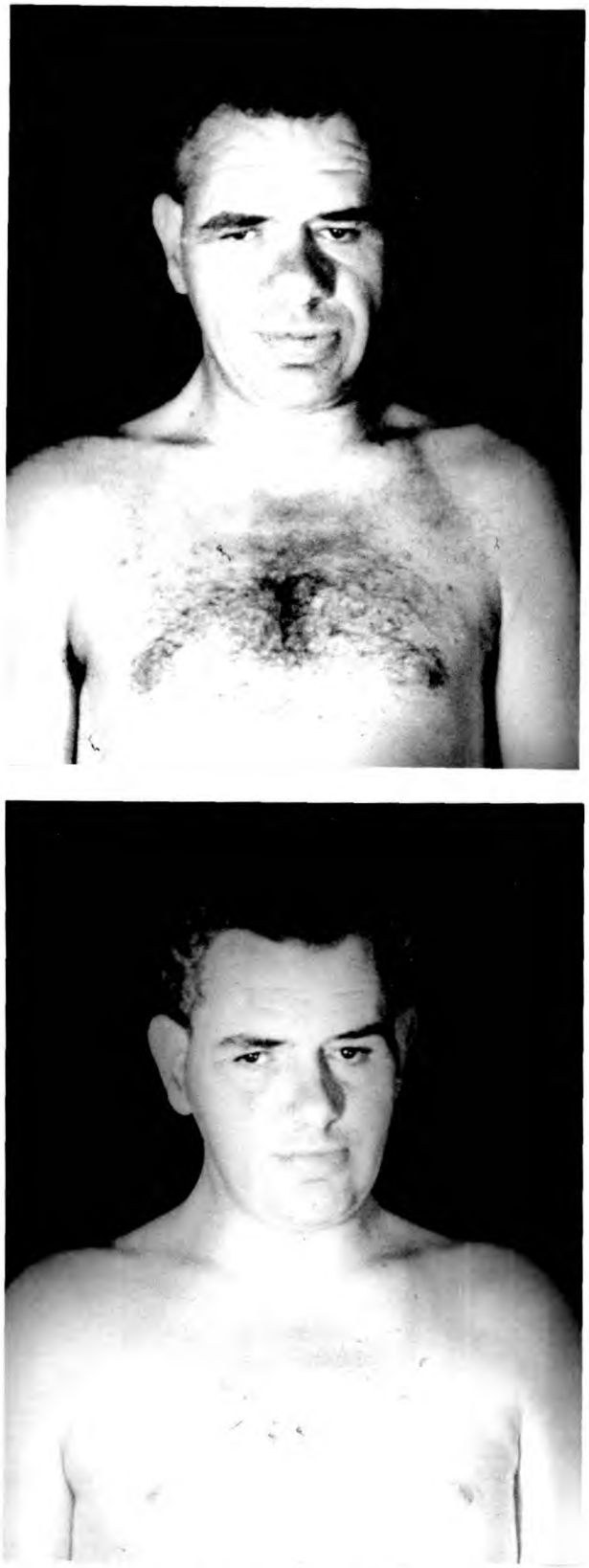

Fig.A.6. Patient **S.Ri.** before implantation (above) and 18 months after implantation (below).

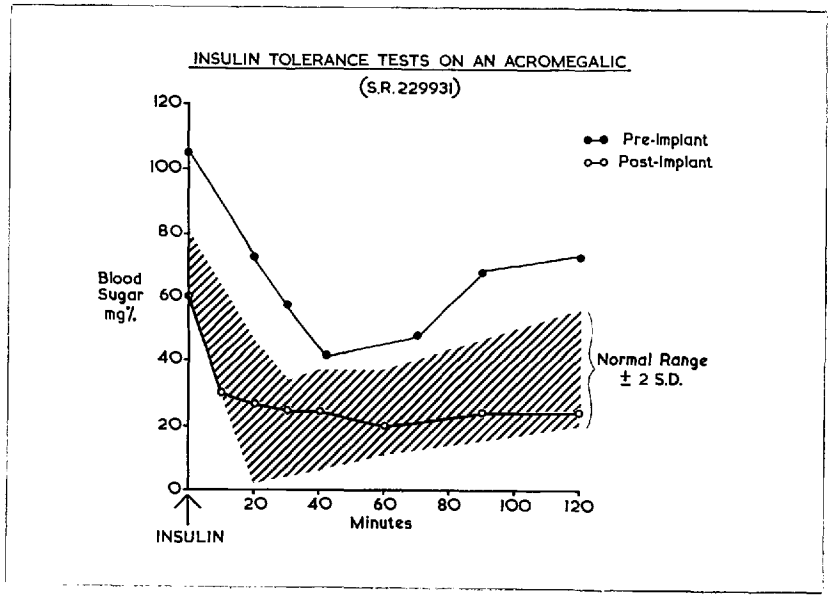

Fig. A.7. The tests were done by injecting soluble insulin intravenously, using a dose of 11.1 units/sq.m. body surface. The initial curve cannot be interpreted as the fasting level was elevated. The second test was entirely within the normal range, but was abnormal in showing no tendency to rise during the second hour, suggesting hypopituitarism.

The urinary calcium had now fallen to normal (12 mEq./day), but he was still in a markedly negative calcium balance (- 12 mEq./day).

Because of his lethargy, and impaired adrenal function tests, he was given cortisone (50mg. daily), and this rapidly restored his energy to normal, and the WDT rose to 80%.

Subsequently, he became clinically myxoedematous, with a low-voltage E.C.G., and was restored with thyroxine. Presumably his pituitary necrosis had progressed. Impotence was satisfactorily treated by monthly injections of 200 mg. testosterone oenanthrate.

At the final assessment three years after implantation, he was in good health, and symptom free. He had lost most of the body hair, and skin thickness appeared normal. The diabetes did not recur, the P.G.T. remained normal, and he progressively lost his acromegalic facies, so that the diagnosis could no longer be made clinically. Hand volumes fell by 50 ml. There was no further enlargement of the pituitary fossa, nor change in acuity. The urinary calcium fell to 8 mEq./day. The radiological thickness of the metacarpal cortex was unchanged at 24 months, but was distinctly reduced at 42 months.

Comment. There was remission of every feature of acromegaly. The headache ceased, the acromegalic facies entirely regressed, the thickness of the metacarpal cortex diminished, and the hypercalcuria ceased. Diabetes mellitus disappeared, and testing for pre-diabetes was twice found to be normal. However, it was unfortunate that a pituitary abscess developed, and this may well have been the cause of greater pituitary destruction occurring than was intended.

APPENDIX II

EFFECT OF PITUITARY IMPLANTATION ON ENDOCRINE EXOPHTHALMOS

Implants were done in six patients with severe eye signs associated with past or present thyrotoxicosis. In no case had there been any improvement on conventional treatment with thyroxine, diuretics and low salt diet. In each case, the dose plan was to deliver 10,000 rads at the normal level of the diaphragma sellae from one or two seeds of Au-198 placed on each side of the mid-line.

There were no complications, and in no instance was pituitary function reduced, either on clinical or test evidence.

The patients were followed up for 3 months to 4 years. The only effect on the eye signs was diminution of congestive features - upper lid oedema, conjunctival oedema, and watering. A significant improvement in these features occurred in three of the six patients over the next few months. There was no improvement in eye muscle paresis as shown by charting of eye movements. Three of the patients were hyperthyroid at the time and none were rendered euthyroid.

Comment

It is very difficult to be sure whether the improvements seen were a direct consequence of implantation, or merely the spontaneous improvement that is often seen with conservative treatment. It is probable that improvement was at least partly attributable to implantation, because all were deteriorating, or at best stationary for some time, and the three patients who showed lessening of the congestive features did so in the few months following operation.

Case J.Vo. This patient was one of the six referred to above. He had never had clinically evident thyrotoxicosis. He was of special interest in having a small pituitary tumour (fossa size on x-ray was 200 sq.mm.), and biochemical hyperparathyroidism. The serum calcium did not fall with partial pituitary ablation. When seen three months later, although there had been slight improvement in the eye congestion, total ablation was done with a second implant of Y-90. He subsequently had a striking

improvement in the eye signs. However, the serum calcium remained abnormal. Two other cases of exophthalmos with pituitary tumour responding to external irradiation have previously been reported (Kate Herman, 1952; Jailer and Holub, 1960).

Literature review.

There are a number of reports on patients with severe exophthalmos treated by pituitary destructive measures. The great majority of these patients were said to have improved. The rationale for this type of treatment has been that the pituitary secretes an exophthalmos-producing substance (EPS) which in some way influences the ocular manifestations of Graves' disease (see later).

External irradiation of the pituitary has been extensively tried. The total doses used have usually been between 3,000 and 4,000 rads. Dobyns collected 37 cases from the literature in 1950 of whom 13 had improved. Reports on a further 30 cases where this has been the main therapeutic measure have been reviewed, and practically all appear to have improved (Herman, 1952; Lamberg, 1957; Jailer and Holub, 1960). However, McCullagh and his colleagues (1957) considered that the extent of improvement after external irradiation was small, and that the method is of doubtful value.

Stalk section with or without pituitary cauterisation was effective in all of 15 reviewed cases, and the more severe the pituitary damage, the better were the results. (Dobyns, 1950; Schneider and Gardner, 1954; McCullagh et al., 1957 and 1960).

Surgical hypophysectomy was effective in all of 7 cases (Albeaux-Fernet et al., 1955; Becker, 1959; Ray 1960; Furth et al., 1962). However, the important finding by Furth and his colleagues (1962) of a patient developing exophthalmos after total hypophysectomy questions an invariable relationship between the pituitary and exophthalmos

More recently, Molinatti and his colleagues (1959) have tried Y-90 pituitary implantation. They treated two patients with very severe exophthalmos, and both showed a dramatic and rapid improvement.

The dose of Y-90 was quite high. In one case a single seed of activity 9 mC was inserted, and in the other, two such seeds. By calculation (based on the Hammersmith Hospital physics data), both these patients must have had very nearly an ablation dose. Neither, in fact, did develop hypopituitarism but both became euthyroid.

The cause of endocrine exophthalmos.

The above findings of an almost invariable improvement in exophthalmos features (as well as frequent loss of hyperthyroidism) following pituitary destructive measures raises the question of the relationship between the pituitary and oculopathy to a practical level.

The mechanism whereby the ocular features of Graves' disease develop is still obscure. Certain aspects have been recently reviewed by McKenzie (1962), and Munro (1962). Although it has for long been known that the injection of anterior pituitary extracts can induce hyperthyroidism and marked exophthalmos resembling that of Graves' disease in animals, especially if thyroidectomised (e.g.Smelser, 1936), TSH assays in humans with Graves' disease have not correlated well with the severity of exophthalmos. Two further substances, exophthalmos-producing-substance (EPS) and long-acting thyroid stimulator (LATS) have been assayed in human serum. Pimstone and colleagues (1963) did parallel assays of TSH, EPS and LATS, and found that the two latter substances showed some correlation with exophthalmos. However, LATS has not yet been found in the human pituitary, and it has persisted after hypophysectomy in patients with Graves' disease (McKenzie, 1962). Thus, the link between the pituitary and exophthalmos is yet to be proven in physiological terms.

Conclusion

From consideration of the above series of patients whose exophthalmos was treated by pituitary destructive measures, the majority of patients probably showed some response. It also appears that the more extensive the pituitary destruction, the better the results. A further trial of Y-90 implantation is therefore warranted. Clearly the ideal treatment

would be to administer an irradiation dose that is short of causing hypopituitarism, and probably the best results would be obtained with a dose that is only a little below this. It is therefore suggested that a suitable implant plan would be to insert two Y-90 rods, whose activity was such as to give a peak dose to the diaphragma sellae of 20,000 rads, and at least 20,000 rads to the remainder of the periphery of the pituitary.

APPENDIX III

SOME MISCELLANEOUS OBSERVATIONS ON PITUITARY IMPLANTATION

The vaginal smear pattern in patients with breast cancer, before and after pituitary implantation.

The purpose of this study was to ascertain whether pituitary destruction would induce any lowering in the "oestrogen level", as indicated by vaginal smear examination, in patients already post-menopausal; in addition, the question of the value of the "oestrogen level" in prediction of breast cancer response was noted.

Patients studied and methods used.

Vaginal smears were examined before and after implantation in six post-menopausal women with breast cancer, by Dr. Erica Wachtel.* The method and normal values were reported by her in 1958. Normal post-menopausal women have a cornification index (C.I.) of under 10 and usually under 5, i.e. less than 5% of 200 consecutive superficial and intermediate squamous cells show pyknotic nuclei. In addition to measuring the C.I., the percentage of basal cells was also reported; this is a further index of oestrogen activity, in that atrophic smears have a higher proportion of basal cells.

Results

(a) Pre-implant C.I. Two to four measurements were made on each of six women. In five, the mean C.I. was under 3.3, and in the sixth (case S.Jo.) it was 11. There was no obvious difference in C.I. between the two patients whose cancer responded and the four who did not respond.

(b) Post-implant C.I. In five of these women, two or more smears were taken after implantation. No change was found in the four whose

* Working in the Institute of Obstetrics and Gynaecology at the Hammersmith Hospital.

pre-implant values were under 3.3. In case S.Jo., there was a clear downward trend from the initial value of 11 to 0·5 (Fig.A.8). She had had a combined adrenalectomy and oophorectomy 36 months previously, having menstruated up to that time; the pituitary implant had been very successful functionally, in that the mean I-131 uptake fell to 8%, and she developed clinical myxoedema with a serum cholesterol of 390mg.% and a very low voltage E.C.G. Her F.S.H. was > 386m.u./day before implantation.

Pre-implant basal cells: Two to four measurements were made in five patients, their mean values being between 0% and 25%.

Post implant basal cells: In the five women, two or more measurements were made. Four (including case S.Jo.) showed clear rises, but one in whom ablation was otherwise functionally complete, remained unchanged.

Discussion

These results show that one patient at least had a significant "oestrogen level" after surgical adrenalectomy and oophorectomy, and this was strikingly reduced after pituitary destruction. The remaining patients had low C.I. values before implantation, and not surprisingly, showed no change.

Case S.Jo. is of particular interest, in that the source of her oestrogen pre-implant must be either an overlooked remnant of ovary (but vide high F.S.H.) or adrenal, or alternatively, the cancer itself. The latter alternative would be consistent with the abnormally high initial level and the fall observed during the striking subjective breast cancer remission; there was no radiological change in the skeletal deposits for the 20 weeks she was followed up. This would be analagous to the frequent finding of a raised C.I. in women with cancer of the genital tract (Wachtel, 1958). It has been well established that oestrogen production sometimes persists in women with breast cancer, following adrenalectomy, oophorectomy, and even hypophysectomy (reviewed by

SERIAL VAGINAL SMEAR EXAMINATIONS IN CASE S. Jo.

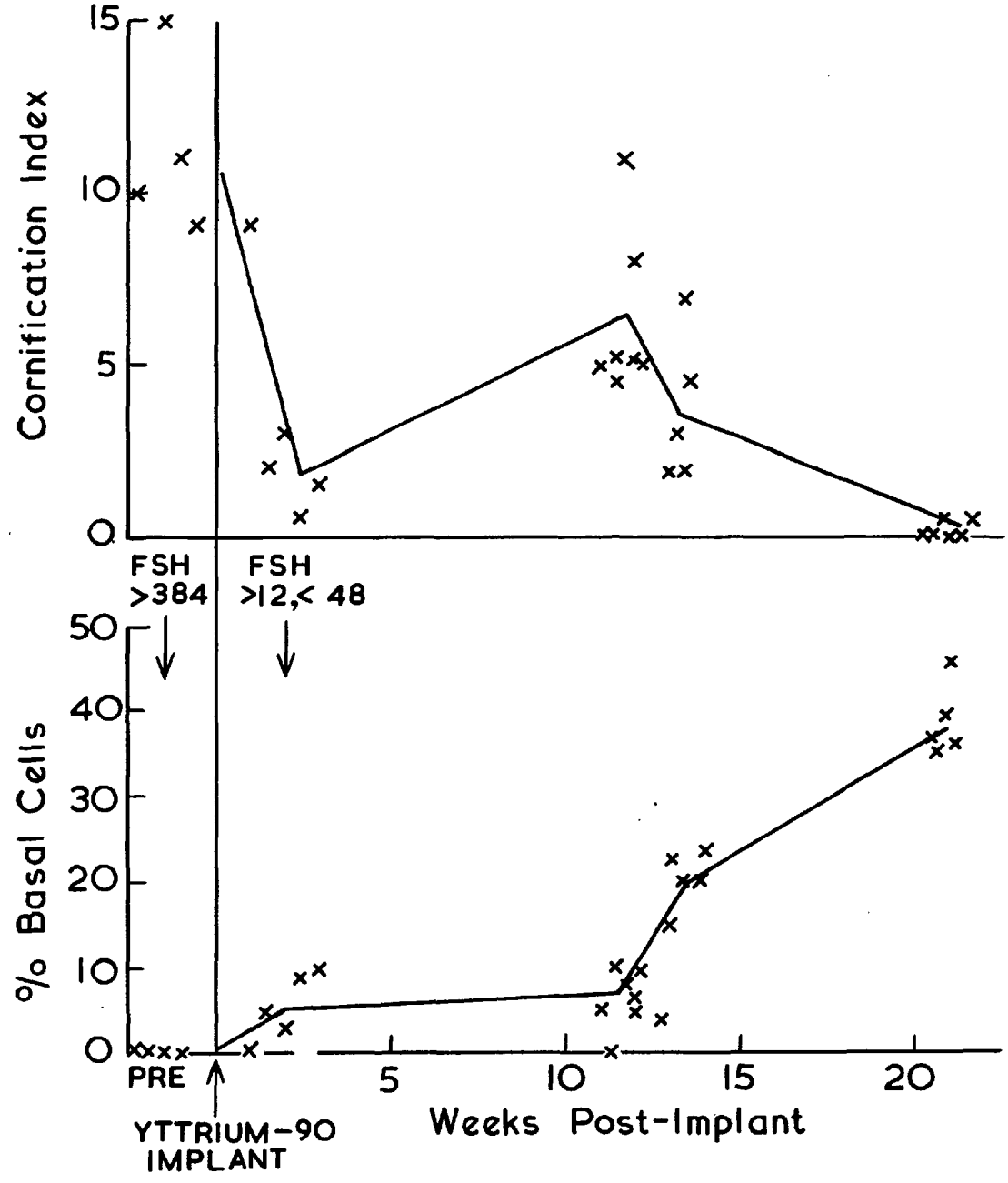

Fig. 8. The patient had had an adrenalectomy and oophorectomy 36 months previously. After implantation, the I-131 uptake fell to 8%.

Swyer et al., 1961).

Vaginal smear data were also reported by Lipsett and Pearson (1956). They followed the effect of hypophysectomy on pre-menopausal women with breast cancer, and found that the pattern showed a post-menopausal picture within a week, and was completely atrophic in two to four weeks; they had not examined the sensitivity of the examination as an index of completeness of ablation.

The present study cannot test the predictive value of the vaginal smear in predicting cancer response, because the pre-implant C.I. showed so little variation. However, Swyer et al. (1961) made a special study of this point in women about to undergo oophorectomy or adrenalectomy. Using chemical methods for various urinary oestrogens and vaginal smear examinations, they found no correlation between cancer response and either the pre-operative oestrogen levels, or the post-operative fall.

Changes in hair and skin; hot flushes.

In no case was there any change in scalp hair, apart from the minor effect of early myxoedema, which was readily reversible.

Axillary and pubic hair usually became more sparse after a year, and by two years, this hair was virtually absent. This was usually not noticed by the patient. The effect on libido could not be investigated in this type of patient, and no patient raised this issue.

The ability to produce a sun-tan was specifically noted, and in no case did this appear to have been altered. Four patients who returned to virtually normal general health and activity were all able to become richly sun-tanned when exposed to the sun over a year after implantation; in all these cases, ablation was functionally complete. It is, however, said ("Textbook of Endorcinology" edited by R. H. Williams, 1962, page 45; "Diseases of the Endocrine Glands", edited by L.J.Soffer, 1956, page 61) that inability to tan is a feature of hypopituitarism. As no change in this respect was noted in the

present study or that of Lipsett and Pearson (1956), it is suggested that this inability is acquired after many years of untreated hypopituitarism with a low ACTH (and presumably MSH) output.

The clinical finding of the lack of hot flushes following pituitary ablation in the only three patients still menstruating at the time of implant in the present series is a well known phenomenon (e.g. Lipsett and Pearson, 1956).

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