Clinical Trials using Various Sodium Fluorides or Related and Similar Compounds

725529 P

(To substitute NaF for Ca gluconate in CIRC IND 4349)

IND 468

2/20/67	Letter to CIRC requesting additional study to IDA	Req 3/14/68
2/26/68	EPC back dip to SHC suggesting application for IND	Rec'd 3/26/68
9/16/69	SHC letter to CIRC requesting approval of study WITH MODIFICATION Reduce daily fluoride dose to 20 mg/day (from 60) Add TBNAA	Acknowledged 4/15/68
9/24/69	CIRC okd request with condition on reduction level. This was acknowledged but not formally tld 9/21/72	SHC 6/30/69 to FDA studies not yet initiated
5/25/71	Reconfiguration Notice returned by SHC 6/9/71 as INACTIVE - 10 patients had been studied	SHC 1/9/73 to FDA notice to reactivate Did not state dose had been reduced
9/7/72) 4/13/72)	SHC to CIRC to reactivate 10C same dose (20 mg) but for 1 years	Did state supplemental for 1 yr instead of 6 mo
12/4/72	to CIRC	No Report
12/13/72	CIRC okd	
12/20/72	EPC - Reactivation dependent on FDA progress report	

The Medical Research Center

Brookhaven National Laboratory

Upton, L. I., New York

REPOSITORY Records Holding Area, Bldg. 494

COLLECTION Committee Clinical Investigations and Uses of Radioisotope

BOX No. 4

FOLDER CIRC #10C

1179609

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

CIRC STATUS MEMO

CIRC No. 10C

Title: Clinical tracer study using sodium fluoride on pts. with senile osteoporosis

To: Dr. Cohn Date: 1/31/74

Please indicate below whether this proposal is continuing or inactive. If continuing, complete the entire form, and attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given), since the last CIRC approval date. Also please add any additional information which may be of use to the Committee in its deliberations. If inactive, merely sign and return this form.

If this form is not returned by 2/28/74, approval of the proposal will automatically be discontinued.

R B Aronson 1/31/74
R.B. Aronson, Ph.D., Associate Chairman Date

To R.B. Aronson,

CIRC PROPOSAL NUMBER 10C IS: Continuing ☐ Inactive ☒

Proposed substantive changes are attached ____

Adverse effects that have not already been reported to the Department Chairman include:
NOT USED IN PAST YEAR!!
SAC

Since the last approval ____ patients have been submitted to the experimental regimen.

The Sponsoring Physician as of this date is ____

The following changes in Investigators should be noted: ____

The following IND #'s have been obtained for specific compounds used in this proposal:

Compound ____ IND # ____ Compound ____ IND # ____

The investigational consent form(s) used in this project are numbered ____ and copies are attached.
Patients involved in this study are referrals from or also studied at the following institution(s)

Attach statement from institution(s) indicating the review committee approval is current.

Signed Martin H. Cohn 2-1-74
Principal Investigator Date

Sponsoring Physician Date

1179610

Form 1970A
CIRC Form 4 3/21/73

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
-90- Upton, New York 11973

NAME

UNIT NO.

CONSENT FOR PROCEDURE, STUDY, OR
DRUG UNDER CLINICAL INVESTIGATION

PAVILION C°

I understand that the physicians at the Hospital of the Medical Research Center, Brookhaven National Laboratory are engaged in research and study of the nature of diseases and of new methods of diagnosis and treatment. I have been informed of the anticipated duration of hospitalization and the nature of the procedure, study, or drug under clinical investigation known as:

Sodium Fluoride IND 4687

I understand that the nature of this procedure, study, or drug is experimental, and that at the present time no assurance can be given that my participation will be directly beneficial to me. I have been informed that the timing and sequence of these studies may not be revealed to me. I understand that in the opinion of the investigators responsible for this project and of the Review Board (Clinical Investigations Committee), I should be informed of the following possible hazards and inconveniences before agreeing to this clinical investigation:

Sodium fluoride is an investigational drug that is being studied in the treatment of a number of bone diseases. To date no serious adverse reactions attributable to sodium fluoride have been reported.

The following subjects have been discussed with the patient by the undersigned:

- the nature, expected duration of treatment and purpose of the administration of this chemical compound.
- the methods and means by which it is to be administered,
- the existence of alternative forms of therapy, if any,
- the possible complications and beneficial effects.

I have been informed of the above. I have also been informed of the customary procedures. These may or may not be used. I have been offered the opportunity for further discussion of this procedure, study, or drug with the attending physician.

I voluntarily consent to participate in the above studies with an understanding of the known possible effects or hazards that might occur in the course thereof, and with the further understanding that not all effects of such procedure, study, or drug are known.

PATIENT'S NAME _____

SIGNED BY: _____
(Patient or Legal Guardian)

WITNESS: _____

I, the undersigned, herewith affirm that I have explained the above to Mr. (Mrs.) (Miss) _____ and I am willing to answer further inquiries.

_____ M.D. DATE _____

Form 1913 -90- 1179611

Effective 5/2/73

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: February 6, 1973

TO: Dr. Aronson

FROM: S. H. Cohn SHC

SUBJECT: INCLUSION OF DR. ZANZI IN ONGOING CLINICAL RESEARCH PROJECTS

I would like to add the name of Dr. I. Zanzi, our new resident collaborator, to the list of physicians participating in the following clinical research projects:

CIRC 10A, 10C, 36, 36A, 36B, 36C, 36D, 36F

51, 54, 61, 67, 72, 78, 79, 86, 87, 88, 91, 96 and 36G that is now in the process of review by the CIRC Committee.

In addition to his own projects, Dr. Zanzi will assume the major part of Dr. Wallach's clinical responsibilities.

SHC:mas

1179612

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

CIRC No. 10C

PURPOSE OF REVIEW:

CLINICAL INVESTIGATION AUTHORIZATION FORM

TITLE:

☐ INITIAL ☒ ADDENDUM

☐ REVISION ☐ RECERTIFICATION

☒ REACTIVATION

CLINICAL TRACER STUDY USING SODIUM FLUORIDE ON PATIENTS WITH SENILE OSTEOPOROSIS

TO CHAIRMAN, CIRC:

THE PROPOSAL FOR CLINICAL INVESTIGATION IDENTIFIED BY THE ABOVE CIRC NUMBER AND TITLE IS FORWARDED HEREWITH FOR REVIEW AND RECOMMENDATION.

R B Aaronson 4 Dec. '72

E.P. ~~Cronkite, M.D.~~, Chairman, Medical Deparment — Date

TO CHAIRMAN, MEDICAL DEPARTMENT:

THE CIRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON 13 December 72 AND RECOMMENDS APPROVAL

WITH THE FOLLOWING MODIFICATIONS:

It is understood that the necessary consent forms for 10A will be signed at the same time as the one for 10C when applicable.

E19613

J.S. Robertson
J.S. ROBERTSON, Chairman

G.C. COTZIAS, Alternate Chairman

Helen A. Connell
H.R. CONNELL

S.H. COHN

Edwin A. Popenoe
E.A. POPENOE, Alternate

R.A. LOVE

Glenn A. Price
G. PRICE

G. CHIKKAPPA

N.P. RATHVON, JR.

D.N. SLATKIN, Alternate

A.P. WOLF, Alternate

TO S.H. Cohn and H.L Atkins

THE ABOVE TITLED AND NUMBERED PROPOSAL IS approved SUBJECT TO THE FOLLOWING:

5/7/73 Replaced by consent 90

Consent forms 74 and/or ~~73~~ to be used for CIRC 10C.
It is noted that there are no progress reports to FDA. Reactivation of this CIRC is dependent on submission of progress reports as required by FDA and their concurrence RPC

(Feb 73 RPC

L.P. Cronkite 20 Dec 1972

E.P. CRONKITE, M.D., Chairman, Medical Department — Date

CIRC Form 1 9/1/72 OK see Cohn memo of 19 Jan 73. NaF at 20mg per day is to be used as described in Am. J. Clin Nut 24, 2024, 1971 RPC

Form 1936A

cc: Dr Dall, A. Harrison, Clinic

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: January 19, 1973

TO: CIRC

FROM: S. H. Cohn SHC

SUBJECT: CIRC 10C and CIRC 96

Enclosed is a copy of the report on fluoride treatment of osteoporosis (CIRC 10C) which was ~~formed~~ forwarded as report to FDA.

I have forwarded a copy of my recent correspondence with FDA which answered the questions raised in their letter to me of December 22, 1972 (CIRC 96).

SHC:mas
Enclosure

Effects of fluoride on calcium metabolism in osteoporosis[1, 2]

S. H. Cohn, C. S. Dombrowski, W. Hauser, and H. L. Atkins

Osteoporosis can be defined as a condition in which the total mass of bone is decreased below the level required for mechanical support (1). This decrease in bone mass in osteoporosis can be considered as a manifestation of an altered dynamic equilibrium resulting from an imbalance between the rates of bone formation and resorption. It is generally believed that, of the two processes, a high resorption rate rather than a low rate of bone formation is responsible for the alteration in bone mass. Rational therapy of osteoporosis thus includes any technique that acts to decrease the rate of bone resorption and maintain Ca homeostasis.

The rationale for the use of fluoride (F) in the treatment of osteoporosis dates at least as far back as 1937, when an epidemiological study made on a population that had a naturally high level of fluoride intake manifested a high rate of osteosclerosis (2). This fluorine-induced osteosclerosis was evidenced by increased trabecular and cortical bone and a thickening of the periosteum. More recently, another roentgenological study of a population on a diet also naturally high in F indicated that this population had a lower incidence of osteoporosis than a similar population on a diet lower in F (3). A third study, in which a population ingesting a high fluoride concentration in the water supply was examined, demonstrated a decreased incidence of osteoporosis in women, as compared with women in a similar population consuming low F levels (4).

On the basis of these observations, a number of investigators have suggested that fluoride, by making bone more resistant to bone resorption stimuli, results in an increased density of the skeleton, and is thus of value in the treatment of metabolic bone diseases characterized by a skeleton depleted of calcium. The mechanism of action of F in decreasing the resorption rate is postulated to be the incorporation of F into the hydroxyapatite crystal of bone. Fluorapatite is presumably more stable and more resistant than hydroxyapatite to parathyroid hormone (PTH), the normal stimulus to resorption (1). A direct action of F on bone cell function, resulting in a decreased osteoclastic activity, has also been postulated (2).

In the past 30 years there has been a large number of clinical studies on patients with various metabolic bone diseases in which the effects of prolonged administration of F (at levels to 200 mg/day) have been quantified. Although a number of investigators have reported F to be effective in the treatment of osteoporosis, as evidenced by a more positive Ca balance and an increase in the bone mass and clinical improvement (5–7), other investigators have failed to discern any positive effect of F on their patients (8, 9).

Thus, the effectiveness of F in the treatment of osteoporosis, even in terms of reduction in bone resorption, has not clearly been established when all of the investigations are considered. Recently, two reviews have been published in this field, (11, 12). The most astonishing fact to emerge is that in the past 35 years over 16,000 papers have been published on the biological effects of fluoride (11). Some of the difficulty encountered in comparing the results of the many investigators can be traced to a lack of commonly accepted indices in the form of distinct biological "endpoints" that can be quantified and measured accurately and, hence, compared meaningfully. Conflicting results are also due to the lack of adequate techniques for quantifying the subtle changes

[1] From the Medical Research Center, Brookhaven National Laboratory, Upton, Long Island, New York.

[2] Research supported by the United States Atomic Energy Commission.

The American Journal of Clinical Nutrition 24: JANUARY 1971, pp. 20–26. Printed in U.S.A.

in bone formation and resorption, and, more importantly, changes in total skeletal mass.

Thus, the present study was designed to quantify changes in skeletal metabolism and bone mass resulting from 2–7 months of F administration in terms of well-defined parameters. For this purpose, three techniques were employed to obtain the requisite data: *1*) a previously established technique of compartmental analysis, based on ^{47}Ca kinetic tracer data, was used to determine values for a number of parameters of Ca metabolism (13); *2*) a Ca balance study was also performed to determine certain parameters of Ca metabolism; *3*) an in vivo neutron-activation analysis technique was used for the determination of total-body calcium, as well as sodium, chlorine, phosphorus, and nitrogen. Thus, changes in the total amounts of these elements occurring as a result of F administration could be determined (14, 15).

Experimental

Patients

Eight patients, 50–86 years of age, with various degrees of osteoporosis, were studied. All of these patients had a major medical problem other than osteoporosis. The osteoporosis was due to disuse atrophy, Parkinsonism, cerebral vascular accidents, neurological deficit, as well as being idiopathic. Six of the patients had been receiving chronic care in a hospital for a period over 3 years. The other two patients, and had sought medical treatment for severe back pain, which was attributed to recent vertebral compression fractures. None of the patients had received hormones in the course of their treatments, nor had they required treatment for an endocrine disorder. Additionally, none of the patients had any history of gastrointestinal disorders, and none presented any unusual dietary history. Only two of the patients, and had received treatment previously for osteoporosis. Two years before the current study they had been given Ca supplements.

Roentgenologic findings for the patients are summarized in Table 1. Because the osteoporosis was localized in certain of the patients, and quite generalized in the others, it was not possible to work out a satisfactory grading system to reflect the severity of the disease for this group of patients.

Calcium balance study

Calcium balance studies were performed on a metabolic ward over a 10-day period following 2 weeks of equilibration with a constant diet of 539 mg Ca and 838 mg P/day. Once the parameters of Ca metabolism were established, the patients were placed on a 20 mg/day supplement of F, admin-

TABLE 1
Clinical description of patients

Subject	Sex	Age	Weight, kg	Clinical diagnosis	Roentgenologic findings
	F	75	48	Primary osteoporosis	Generalized bone demineralization, ballooned disks and one compressed vertebral fracture
	F	81	60	Primary osteoporosis	Generalized bone demineralization, ballooned disks and one compressed vertebral fracture
	F	61	53	Primary osteoporosis, Parkinsonism, chronic pyelonephritis	Severe generalized bone demineralization, several healed rib fractures, three compressed vertebral fractures
	F	71	70	Primary osteoporosis, Parkinsonism	Paget's disease of skull, ballooned disks and one compressed vertebral fracture, several healed rib fractures
	F	50	69	Regional osteoporosis, due to right hemiplegia after frontoparietal craniotomy, "spontaneous" rib fracture	Marked demineralization of right humerus, right hemipelvis and right lower extremity
	M	57	66	Regional osteoporosis, due to incomplete tetraplegia following automobile accident	Marked demineralization of left shoulder girdle and left hip, one healed rib fracture
	M	86	76	Old CVA with hemiplegia, osteoarthritis, disuse osteoporosis	Moderate generalized bone demineralization, ballooned disks and one vertebral fracture
	M	62	72	Old CVA with right hemiplegia, disuse osteoporosis	Slight demineralization of lumbodorsal spine with two ballooned disks

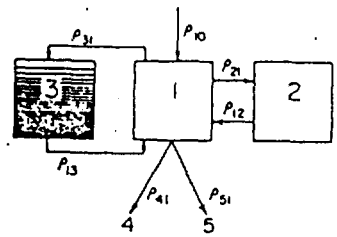

FIG. 1. Compartmental model of calcium kinetics. Compartments are designated as follows: *1)* Physiological pool of calcium in isotopic equilibrium within 1 hr (plasma–extracellular–intracellular). *2)* Physiological pool of calcium in isotopic equilibrium within 2 days (exchangeable bone). *3)* Calcium in "deep bone" or very slowly exchanging bone. The transfer rates, ρ, are designated as follows: $\rho 10$ = Ca intake rate; $\rho 12$ = Ca flow rate into *compartment 1* from exchangeable bone; $\rho 21$ = Ca flow rate into exchangeable bone from *compartment 1;* $\rho 13$ = rate of resorption and slow exchange from bone; $\rho 31$ = rate of accretion into bone; $\rho 41$ = urinary calcium excretion rate; and $\rho 51$ = fecal calcium excretion rate.

istered as an enteric coated capsule 3 times daily with meals.

On the basis of the data of Spencer (16), who demonstrated a very positive fluoride balance (5.3 mg/day) with doses as low as 9.3 mg/day, the level of F administered in this study was set at 20 mg/day. Even though no toxic effects were noted in previous studies (11, 12), it was considered prudent to use the smallest dose consistent with the attainment of the desired effects.

After 2 months of F administration, the balance study was repeated. Five of the patients then returned home and continued taking the F supplement for an additional 5 months. Sample diets were analyzed to determine the levels of Ca and P. Urine and stool samples (24-hr output) were analyzed for Ca and P by atomic-absorption techniques (17).

Calcium 47-tracer kinetic study

During both 10-day balance studies a tracer kinetic study was also performed. Each patient was injected intravenously with 20 μCi high specific activity $^{47}CaCl_2$. Blood samples were collected at 1 and 6 hr and daily for 10 days. Calcium 47 was measured on all the 24-hr samples of urine and stool with standard counting techniques described previously (17). The patients were counted daily in the Brookhaven whole-body counter for direct measurement of the retention of ^{47}Ca (17).

Compartmental analysis

The details of the compartmental analysis and model employed have been previously described (13, 17). The Berman simulation, analysis, and modelling (SAAM) program (modified for the CDC-6600) was used for the calculation of the parameters of the mathematical model. The model and the description of the various compartments and flow rates are presented in Fig. 1. Both the sizes of the compartments and the flow rates between the compartments are calculated before and after the period of F administration.

In vivo neutron activation analysis

Before, during, and after the fluoride treatment, total-body levels of Ca, Na, Cl, P, and N were measured by a whole-body in vivo neutron-activation technique (14, 15). In addition, total-body K (^{40}K) was determined by whole-body counting. After 2 months of F treatment, the activation analysis was performed on all eight patients. At the termination of the study (after 3 or 7 months of F supplementation), the total-body levels of the above elements were again determined by the activation technique for all patients.

The somewhat greater variability in the precision of the results obtained here, compared with previous studies (14, 15), is probably due to the difficulties experienced with these patients in achieving a precise measure of the neutron-irradiation flux measurement. Because of the presence of fractures, the obesity of several of the patients, and the poor posture resulting from both hemiplegia and osteoporosis, it was extremely difficult to reproduce the exposure geometry, and hence the dosimetry measurement (as determined by dosimeters placed on the patient's body) also varied (14, 15). To minimize this variability, values for the total-body levels were normalized to the patient's total-body sodium. It was assumed, of course, that the patient's Na did not change between measurements, and thus that the induced ^{24}Na activity serves as a biological dosimeter of the actual thermal neutron flux to which the patient was bilaterally exposed.

One patient (because of his excessive corpulence and the total paralysis of his legs, could not be bilaterally exposed with the present set-up as is required by the calibration technique. His measurements are thus for a unilateral exposure and, therefore, are not absolute; nevertheless, they can be considered precise in terms of his control measurements obtained in the identical exposure geometry.

It should be emphasized that although the Ca, Na, and Cl measurements are absolute, the measurements of N and P are only relative. Briefly, this situation is the result of the nonuniformity of neutron-depth flux through the body of unmoderated fast neutrons responsible for the production of P and N. The Ca, Na, and Cl, on the other hand, are the products of a thermalized fast neutron beam that is quite uniform in flux density through the body and thus more easily calibrated for the measurement of the absolute value (14, 15).

Results

The computer-derived values for the various parameters of calcium metabolism in

TABLE 2
Effect of fluoride on the parameters of calcium metabolism

Subject	Compartment size, g			Transfer rates, g/day			
	1	2	1 + 2	Urine $\rho 41$	Stool $\rho 51$	Accretion $\rho 31$	$\rho 12,21$
Control							
	1.83 ± 0.11	2.50 ± 0.17	4.33 ± 0.18	0.109 ± 0.003	0.072 ± 0.003	0.431 ± 0.005	6.36 ± 0.75
	1.50 ± 0.46	2.47 ± 0.31	3.97 ± 0.43	0.024 ± 0.001	0.097 ± 0.001	0.520 ± 0.009	15.35 ± 8.45
	1.46 ± 0.12	2.24 ± 0.18	3.70 ± 0.18	0.068 ± 0.002	0.092 ± 0.005	0.472 ± 0.006	6.26 ± 0.96
	1.92 ± 0.14	2.28 ± 0.21	4.20 ± 0.25	0.178 ± 0.007	0.061 ± 0.004	0.302 ± 0.009	3.01 ± 0.54
	2.42 ± 0.23	1.95 ± 0.36	4.36 ± 0.55	0.180 ± 0.009	0.319 ± 0.003	0.647 ± 0.011	1.18 ± 0.28
	1.88 ± 0.15	1.58 ± 0.23	3.46 ± 0.35	0.089 ± 0.005	0.066 ± 0.002	0.259 ± 0.008	1.30 ± 0.28
	1.63 ± 0.15	1.85 ± 0.18	3.48 ± 0.29	0.020 ± 0.001	0.093 ± 0.006	0.472 ± 0.006	3.77 ± 0.75
	2.69 ± 0.38	2.32 ± 0.81	5.00 ± 1.21	0.063 ± 0.007	0.109 ± 0.013	0.325 ± 0.019	8.61 ± 0.12
After NaF treatment							
	2.32 ± 0.20	2.92 ± 0.35	5.24 ± 0.49	0.076 ± 0.004	0.059 ± 0.004	0.436 ± 0.007	5.25 ± 0.96
	2.36 ± 0.41	2.47 ± 0.29	4.83 ± 1.22	0.023 ± 0.004	0.072 ± 0.011	0.357 ± 0.014	1.90 ± 0.47
	2.05 ± 0.20	2.04 ± 0.36	4.09 ± 0.54	0.040 ± 0.003	0.052 ± 0.005	0.366 ± 0.007	1.69 ± 0.34
	2.02 ± 0.30	1.63 ± 0.32	3.65 ± 0.58	0.075 ± 0.006	0.066 ± 0.007	0.295 ± 0.012	3.89 ± 1.30
	2.04 ± 0.16	2.60 ± 0.36	4.65 ± 0.49	0.130 ± 0.006	0.057 ± 0.005	0.633 ± 0.009	1.26 ± 0.17
	1.83 ± 0.19	1.54 ± 0.17	3.37 ± 0.26	0.071 ± 0.002	0.035 ± 0.002	0.417 ± 0.004	5.54 ± 1.61
	1.99 ± 0.29	1.81 ± 0.35	3.80 ± 0.31	0.027 ± 0.001	0.084 ± 0.005	0.537 ± 0.006	4.34 ± 2.20
	2.00 ± 0.27	1.76 ± 0.23	3.76 ± 0.35	0.076 ± 0.003	0.067 ± 0.005	0.495 ± 0.007	4.22 ± 1.62

Compartments: (*1*) plasma, extracellular, intracellular Ca space; (*2*) exchangeable bone. Transfer rates: $\rho 31$—accretion rate into bone; $\rho 41$—urinary Ca excretion; $\rho 51$—fecal Ca excretion rate; $\rho 21$—Ca flow rate into exchangeable bone; $\rho 12$—Ca flow rate into *compartment 1* from *2*.

each patient before and after the 2 months of fluoride supplementation are presented in Table 2. There is no consistent change in the sizes of readily exchangeable *compartments 1* and *2*. In five patients there was an increase in the total exchangeable pool, whereas in the other three patients there was a decrease as a result of the F administration. The urinary excretion rate ($\rho 41$) and the fecal excretion rate ($\rho 51$) generally decreased as a result of F administration. In half the patients the accretion rate ($\rho 31$), which reflects the rate of movement of Ca into bone, increased slightly; however, in the other patients there was a fall in the accretion rate.

The results of the stable Ca balance studies are shown in Table 3. The stable urinary and fecal Ca excretion generally decreased after 2 months of F supplementation. The calcium balance thus showed a slight increase in most patients. At all times during the experimental period and following administration of F, the levels of Ca and P in the plasma were within normal range (Table 3). There was an increase in the alkaline phosphatase activity in most of the patients on the F supplement.

Further data on the excretion and retention of ^{47}Ca after 2 months of F supplementation are summarized in Table 4. The retention of ^{47}Ca in each patient, as measured by excretion, is seen to correlate fairly well with the retention as determined by whole-body counting. The whole-body retention of ^{47}Ca seems to be generally higher following F administration.

The results of the in vivo neutron activation analysis normalized to the total-body sodium are presented in Table 5. The total-body Ca level after 2–7 months of F supplementation showed no significant change. The change in Ca level in each patient compared with the respective control level was on the average ±3.5%. In one patient ( ) there was a decrease of borderline significance (6.1%) in the total-body Ca after 2 months of F. The net result, however, is that there is no marked change in the total-body Ca or P following either the 2 months or the 7 months of F supplementation. There is no obvious explanation for the high P level noted in the first count on one patient ( ).

The total-body nitrogen increased only in those patients on F for 7 months. The Na

TABLE 3
Mean urine, stool, and plasma values over 10-day study period following fluoride administration

Subject		Urine calcium, mg/24 hr	Stool calcium, mg/24 hr	Resorption[a] ρ13, mg/24 hr	Calcium balance, mg/24 hr	Urine phosphorus, mg/24 hr	Plasma calcium, mg/100 ml	Plasma phosphorus, mg/100 ml	Alkaline phosphatase units
	Pre	174	358	295	7	595	9.7	2.26	3.8
	Post	105	360	221	74	578	9.6	2.39	5.8
	Pre	114	353	359	72	428	9.3	3.20	4.4
	Post	80	333	310	126	326	9.1	3.18	5.9
	Pre	82	454	469	3	484	8.9	3.09	5.8
	Post	55	440	421	55	490	8.8	3.27	12.1
	Pre	45	407	433	87	439	9.0	2.40	8.4
	Post	37	439	294	63	418	8.9	2.50	11.1
	Pre	134	239	485	166	581	9.3	2.93	7.0
	Post	128	277	499	134	571	9.4	3.45	5.8
	Pre	89	435	244	15	505	9.1	2.93	5.8
	Post	67	358	303	114	494	8.6	2.52	6.7
	Pre	106	345	237	88	480	9.8	3.40	5.2
	Post	68	322	346	149	435	9.4	2.87	4.9
	Pre	31	387	351	121	439	9.0	2.93	8.3
	Post	30	369	397	140	485	8.9	2.79	12.4

[a] Resorption (ρ13) = absorption (ρ10) − (accretion (ρ31) + urinary Ca (ρ41) + endogenous fecal excretion (ρ51)).

and Cl concentrations were relatively constant. The variation observed in Na was ascribed primarily to the difficulties in reproducing the geometry of the dosimeters used to monitor the patients' neutron exposure, as previously discussed.

Clinical and radiographic studies

The clinical response in the eight patients is difficult to evaluate because of its subjective nature. However, whereas high Ca feeding produced a positive subjective response and the expressed feeling of a decrease in bone pain, F administration did not evoke a positive subjective response. The incidence of spontaneous fractures did not decrease during the 7 months of F administration. One patient (___ complained of a painful ankle after several months of F, at which time the F administration was discontinued. It is possible that the pain could be attributed to an inflammatory reaction produced by the concentration of F in joint cartilage and tendon (5, 7, 9). Roentgenograms showed suggestive new bone formation about the distal tibia, possible evidence of fluorosis. Another patient (___) complained of exacerbation of previously noted pain in the elbow during F therapy. No other deleterious effects of F were observed.

No significant change in bone density, as evidenced by radiography, was noted during the F treatment.

Discussion

The increase in the Ca balance noted from the stable Ca data averaged 50 mg/day. If the errors inherent in the Ca balance technique are considered, this increase can only be considered as suggestive of a significant effect of fluoride. The more positive Ca balance is presumably the result of a decreased excretion of Ca. The increased retention of Ca following F administration is also evidenced by the ^{47}Ca whole-body counting data.

More information on the dynamic changes in Ca metabolism can be deduced from the ^{47}Ca kinetic data. The only significant F-in-

TABLE 4
Excretion and retention of ^{47}Ca, 10 days postinjection

Subject	Urine, %	Stool, %	Excretion, %	Retention, %	Retention by whole-body counting, %
Control					
	13.82	8.59	22.41	77.59	79.26
	3.20	12.18	15.38	84.62	88.57
	9.26	11.58	20.84	79.16	80.27
	22.85	8.11	30.96	69.07	69.69
	15.34	3.02	18.36	81.64	86.56
	14.90	9.61	24.51	75.49	77.02
	2.74	12.70	15.44	84.56	85.00
	8.21	14.19	22.40	77.60	80.86
After NaF supplementation					
	9.47	6.48	15.95	84.05	83.08
	3.16	9.91	13.07	86.93	88.47
	6.03	6.87	12.90	87.10	85.99
	12.88	10.58	23.46	76.54	81.03
	12.84	1.14	13.98	86.02	86.56
	10.56	4.93	15.49	84.51	85.00
	3.99	12.32	16.31	83.69	85.00
	9.05	12.06	21.11	78.89	79.92

duced change here is a decrease in the urinary excretion and endogenous fecal excretion rates. Incidentally, the close correspondence between the stable urine Ca excretion value and the value (ρ41), calculated from the compartmental analysis, verifies the accuracy of the computer solution of the compartmental model. There is no indication that fluoride significantly affects the size of the exchangeable Ca *compartments 1* and *2*, as reported by Lukert et al. (9). The mechanism postulated for the effects of fluoride assumes an increased crystallinity of fluoride-containing bone. According to the theory, the increased crystallinity should reduce the reactivity by providing less surface for deposition (9). If this theory holds, the size of the exchangeable Ca compartment should have been affected by the F. The absence of an effect of F on the bone accretion rate, as noted here, corroborates the findings reported by Lukert and coworkers (9) and indicates that no significant increase takes place in new bone formation.

The variability of the balance data lies in the interrelationship of bone resorption and bone accretion. Some of the conflicting data resulting from F administration reported in the literature probably derive from the observation that F not only inhibits resorption, but also stimulates PTH, thus initiating new bone formation (18). Other studies involving the administration of F to rats (19) have failed to demonstrate parathyroid stimulation, but this may be the result of species specificity. Apparently F does not act as a generalized depressant on all bone-resorbing cells, but rather appears to affect only the resorption of fluoride-containing bones. Also, fluoride appears to act on the parathyroids directly and thus produces an increase in the resorption of normal (i.e., fluoride-free) bones as a compensatory response to maintain serum Ca at a constant level (18). This increase in bone resorption is also seen histologically in a nonhomogeneous anatomical distribution (7).

Hyperactivity of PTH could account for the increased number of resorption cavities with fibrous tissue replacement and also the increased deposition of periosteal bone observed in some patients after several months of fluoride treatment.

The increase in plasma alkaline phosphatase observed in this study and as previously noted (12), may reflect a fluoride-induced regeneration of new bone.

The most accurate measure of the change in total-body calcium is that obtained by whole-body neutron activation. After 2–7

TABLE 5
In vivo neutron-activation analysis of osteoporotic patients treated with fluoride

Subject	Duration of fluoride administration, months	N, g	P, g	Cl, g	Na, g	Ca, g	K, g
	0	2,327	646	60	76	752	69.7
	2	2,007	437	63	76	720	71.6
	3	2,171	410	65	76	716	
	0	2,243	402	62	75	685	65.1
	2	2,171	383	67	75	660	65.4
	5.5	2,128	384	70	75	705	
	0	2,233	364	72	75	637	60.1
	2	2,000	365	81	75	622	62.0
	3	1,942	358	77	75	645	
	0	2,332	420	68	70	734	66.6
	2	2,342	385	72	70	689	67.7
	0	2,765	575	77	95	1,000	92.1
	2	3,325	631	84	95	977	92.9
	7	3,198	556	87	95	1,025	89.6
	0	2,502	551	70	86	949	104.6
	2				86	997	113.8
	7	3,021	561	70	85	983	109.8
	0	1,971	358	71	79	620	77.4
	2	1,748	445	78	79	603	81.8
	7	2,183	358	71	79	603	
	0	1,890	457	65	80	778	81.9

was administered. The significance of the increase in nitrogen concentration that appeared in most of the patients after 7 months of F supplementation (also noted by Lukert (9)) is not obvious.

The failure of the calcium balance to change more significantly may be due to the relatively low levels of F employed or the short duration of the study, or both. Rich et al. (5), for example, reported that changes in the Ca balance in one patient occurred only after 32 weeks of treatment with 45–70 mg/day of fluoride. Rich and Ivanovich (6) have stressed the necessity of using the lowest effective dose of F because of the possibility of nonskeletal toxicity. Since the lowest effective dose level of F has not been established, they have used 0.5 mg F/kg body wt. However, Bernstein (7) reported beneficial effects in terms of Ca balance, X-ray diffraction analysis, and bone histology, with levels of fluoride as low as 22 mg/day.

The fluoride concentration used in the present study was approximately that of the population studied by Roholm (2). However, it is to be noted that the osteosclerotic changes observed in the latter study did not appear until about 5 years after the initiation of F feeding. Purves (21) has reported beneficial effects of F in treating patients with Paget's disease at approximately the levels of

long period of time. A change in the rate of spontaneous fracture is a somewhat more objective guide. The final judgment must be made, of course, on how well the patient maintains the beneficial improvement over a very long period of time. By all of these criteria, fluoride treatment, as described here, cannot be considered as effective a therapeutic agent as a high calcium diet (17).

Cohen (12) has stressed the need for Ca supplementation and has suggested that the effects of a high Ca diet would be synergistic with fluoride. It is possible that, although fluoride may favor mineralization, administration of a surfeit of Ca and possibly PO_4 may be the only way to realize the full potential of the stimulus to bone formation.

Fluoride appears to decrease slightly the rate of development of osteoporosis in terms of slowing the loss of Ca from the body. In this sense, fluoride taken over an extended period may act to diminish the morbidity of osteoporosis. The epidemiological studies of populations living in areas with high F concentration indicate that some beneficial effects can be obtained. However, it must be emphasized that these latter populations have undergone extremely long periods of fluoride ingestion, and, perhaps even more importantly, the F was incorporated into the bone when the individual was young and the rate of bone growth and turnover was very high. It may be that F is useful in the prevention of the development of osteoporosis, aside from its potential therapeutic effects.

Conclusion

Kinetic tracer techniques providing data for a compartmental analysis were supplemented with calcium-balance measurements to provide information on the rate of Ca resorption, endogenous fecal excretion, size of exchangeable Ca pools, and accretion rates in eight osteoporotic patients. With each patient acting as his own control, the effect of fluoride administration (20 mg/day) was measured in terms of the above parameters of skeletal metabolism.

The kinetic study indicated no significant change in the size of the exchangeable calcium pools or in the accretion rate following administration. There was a slight increase in ^{47}Ca retention as a result of F supplementation. After 2–7 months of fluoride treatment, there was no significant increase in total-body Ca as measured by the in vivo neutron-activation technique. Based on these results and on clinical observations, fluoride cannot be considered to be an effective treatment for osteoporosis. Since the response to fluoride is very slow, however, it may be that considerably longer periods of treatment and observation are required for an adequate assessment of the efficacy of fluoride treatment.

The authors wish to thank Drs. S. Scaffidi, G. Marsh, M. Cottrell and X. Damianos for the referral of the patients for this study. In addition, the authors are indebted to Dr. S. Scaffidi for his participation in the clinical care of the patients.

References

1. HEANEY, R. P. A unified concept of osteoporosis. *Am. J. Med.* 39: 877, 1965.
2. ROHOLM, K. *Fluorine Intoxication, A Clinical-Hygienic Study*. London: Lewis, 1937.
3. LEONE, N. C., C. A. STEVENSON, T. F. HILBUSH AND M. C. SOSMAN. A roentgenographical study of a human population exposed to high fluoride domestic water: a 10-year study. *Am. J. Roentgenol. Radium Therapy Nucl. Med.* 74: 874, 1955.
4. BERNSTEIN, D. S., N. SADOWSKY, D. M. HEGSTED, C. D. GURI AND F. J. STARE. Prevalence of osteoporosis in high- and low-fluoride areas in North Dakota. *J. Am. Med. Assoc.* 198: 499, 1966.
5. RICH, C., J. ENSINCK AND P. IVANOVICH. The effects of sodium fluoride on calcium metabolism of subjects with metabolic bone disease. *J. Clin. Invest.* 43: 545, 1964.
6. RICH, C., AND P. IVANOVICH. Response to sodium fluoride in severe primary osteoporosis. *Ann. Internal Med.* 63: 1069, 1965.
7. BERNSTEIN, D. S., AND P. COHEN. Use of sodium fluoride in the treatment of osteoporosis. *J. Clin. Endocrinol. Metab.* 27: 197, 1967.
8. ROSE, G. A. A study of the treatment of osteoporosis with fluoride therapy and high calcium intake. *Proc. Roy. Soc. Med.* 58: 436, 1965.
9. LUKERT, B. P., J. C. MEEK AND R. E. BOLINGER. Acute effects of fluoride on ^{47}calcium dynamics in osteoporosis. *J. Clin. Endocrinol. Metab.* 27: 828, 1967.
10. HIGGINS, B. A., J. R. NASSIM, R. ALEXANDER AND A. HILB. Effect of sodium fluoride on calcium, phosphorus and nitrogen balance in patients with Paget's disease. *Brit. Med. J.* 1: 1159, 1965.

11. FACCINI, J. M. Fluoride and bone, a review. *Calcified Tissue Res.* 3: 1, 1969.
12. COHEN, P., G. L. NICHOLS AND H. H. BANKS. Fluoride treatment of bone rarefaction in multiple myeloma and osteoporosis, a review. *Clin. Orthopaed. Related Res.* 64: 221, 1969.
13. COHN, S. H., S. R. BOZZO, J. E. JESSEPH, C. CONSTANTINIDES, D. R. HUENE AND E. A. GUSMANO. Formulation and testing of a compartmental model for calcium metabolism in man. *Radiation Res.* 26: 319, 1965.
14. COHN, S. H., C. S. DOMBROWSKI AND R. G. FAIRCHILD. *In-vivo* activation analysis of calcium in man. *Intern. J. Appl. Radiation Isotopes* 21: 127, 1970.
15. COHN, S. H., AND C. S. DOMBROWSKI. Measurement of total-body calcium, sodium, chlorine, nitrogen and phosphorus in man by *in-vivo* neutron activation analysis. *J. Nucl. Med.* In press.
16. SPENCER, H., I. LEWIN, J. FOWLER AND J. SAMACHSON. Effect of sodium fluoride on calcium absorption and balance in man. *Am. J. Clin. Invest.* 22: 381, 1969.
17. COHN, S. H., C. S. DOMBROWSKI, W. HAUSER AND H. L. ATKINS. High calcium diet and the parameters of calcium metabolism in osteoporosis. *Am. J. Clin. Nutr.* 21: 1246, 1968.
18. FACCINI, J. M. Inhibition of bone resorption in the rabbit by fluoride. *Nature* 214: 1269, 1967.
19. RAISZ, L. G., AND D. R. TAVES. The effect of fluoride on parathyroid function and responsiveness in rats. *Calcified Tissue Res.* 1: 219, 1967.
20. CASS, P. M., J. D. CROFT, P. PERKINS, W. NYE, C. WATERHOUSE AND R. TERRY. New bone formation in osteoporosis following treatment with sodium fluoride. *Arch. Internal Med.* 118: 111, 1966.
21. PURVES, M. J. Some effects of administering sodium fluoride to patients with Paget's disease. *Lancet* 2: 1188, 1962.

Minutes CIRC Meeting

13 December 1972

Present: J.S. Robertson, H.R. Connell, R.A. Love, E.A. Popenoe, G.A. Price

Absent: S. Cohn, G. Chikkappa, N.P. Rathvon, Jr.

The meeting was held in the Small Conference Room of the Medical Research Center. Dr. Robertson opened the meeting at 1400.

The minutes of the previous meeting, 11 December 1972 were accepted as distributed.

CIRC #95 was reviewed first. Dr. Atkins was invited into the Conference Room to answer questions raised by the Committee. CIRC #95 was approved subject to the following changes agreed to by Dr. Atkins:

1. Clarification of pertinent statements to remove ambiguity as to whether pregnant females will be excluded unconditionally.
2. The dose for normal subjects will be 1/10 or less of the dose stated in the proposal for subjects with malignancies.
3. The Consent Form should contain a statement that a radiation dose will be received and relate the dose to accepted procedures.

CIRC #96 was approved subject to these provisos:

1. It is requested that in the case where a patient will have to sign more than one Consent Form, all the appropriate Consent Forms will be signed at the same time.
2. It is recommended that an estimate of the radiation dose from the skeletal survey be included in the cumulative dose record in the patient's chart.

CIRC #7 was approved for recertification. However, it is noted that the previous requirement that ^{13}C be included in Consent Form #30 has not been implemented and it is requested that this be done.

The following proposals were reviewed and approved for recertification:

CIRC #26
#27 and #27A
#46
#57
#77

CIRC #10C was reviewed next and approved for reactivation with the condition that when applicable, the necessary Consent Form for 10A will be signed at the same time that the Consent Form for #10C is signed.

The Committee considered next Dr. S.H. Cohn's memorandum to Dr. J.S. Robertson of 12/12/72 re CIRC #91. The questions raised by the Committee on 11 December 1972 concerning proposal #91 were found to be satisfactorily answered by this memorandum and CIRC #91 was approved.

The meeting was adjourned at 1630.

Respectfully submitted

Helen R. Connell

Helen R. Connell

1179624

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: December 4, 1972

TO: CIRC Committee (Dr. Robertson)

FROM: R.B. Aronson, Ph.D. R B Aronson

SUBJECT: CIRC Meeting

The following proposals are attached for your consideration at the CIRC meeting scheduled for December 11, 1972 in the Small Conference Room at 2:00 PM:

Initial: CIRC 91
92
93
94
95
96

Recertification: CIRC 7
26
27 & 27A
46
57
77

Reactivation: CIRC 10C

RBA/ck
ENC.

1179625

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973
-73-

NAME

UNIT NO.

CONSENT FOR PROCEDURE, STUDY, OR DRUG UNDER CLINICAL INVESTIGATION

PAVILION OP

I understand that the physicians at the Hospital of the Medical Research Center, Brookhaven National Laboratory are engaged in research and study of the nature of diseases and of new methods of diagnosis and treatment. I have been informed of the anticipated duration of hospitalization and the nature of the procedure, study, or drug under clinical investigation known as:

Sodium Fluoride IND 4687

I understand that the nature of this procedure, study, or drug is experimental, and that at the present time no assurance can be given that my participation will be directly beneficial to me. I have been informed that the timing and sequence of these studies may not be revealed to me. I understand that in the opinion of the investigators responsible for this project and of the Review Board (Clinical Investigations Committee), I should be informed of the following possible hazards and inconveniences before agreeing to this clinical investigation:

Sodium fluoride is an investigational drug that is being studied in the treatment of a number of bone diseases. To date no serious adverse reactions attributable to sodium fluoride have been reported.

The following subjects have been discussed with the patient by the undersigned:

-the nature, expected duration of treatment and purpose of the administratio of this chemical compound.
-the methods and means by which it is to be administered,
-the existence of alternative forms of therapy, if any,
-the possible beneficial effects.

I have been informed of the above. I have also been informed of the customary procedures. These may or may not be used. I have been offered the opportunity for further discussion of this procedure, study, or drug with the attending physician.

I voluntarily consent to participate in the above studies with an understanding of the known possible effects or hazards that might occur in the course thereof, and with the further understanding that not all effects of such procedure, study, or drug are known.

PATIENT'S NAME _____

SIGNED BY: _____
(Patient or Legal Guardian)

WITNESS: _____

I, the undersigned, herewith affirm that I have explained the above to Mr. (Mrs.) (Miss) _____ and I am willing to answer further inquiries.

_____ M.D. DATE _____

5/2/73 Replaced by Consent #90

Form 1913 -73-

1179626

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973
-74-

NAME

UNIT NO

CONSENT FOR PROCEDURE, STUDY, OR
DRUG UNDER CLINICAL INVESTIGATION

PAVILION OP

I understand that the physicians at the Hospital of the Medical Research Center, Brookhaven National Laboratory are engaged in research and study of the nature of diseases and of new methods of diagnosis and treatment. I have been informed of the anticipated duration of hospitalization and the nature of the procedure, study, or drug under clinical investigation known as:

Study of Calcium Kinetics (^{47}Ca)

I understand that the nature of this procedure, study, or drug is experimental, and that at the present time no assurance can be given that my participation will be directly beneficial to me. I have been informed that the timing and sequence of these studies may not be revealed to me. I understand that in the opinion of the investigators responsible for this project and of the Review Board (Clinical Investigations Committee), I should be informed of the following possible hazards and inconveniences before agreeing to this clinical investigation:

The radiation exposure to the individual is very small. There may be a minor discomfort associated with the taking of blood samples.

I have been informed of the above. I have also been informed of the customary procedures. These may or may not be used. I have been offered the opportunity for further discussion of this procedure, study, or drug with the attending physician.

I voluntarily consent to participate in the above studies with an understanding of the known possible effects or hazards that might occur in the course thereof, and with the further understanding that not all effects of such procedure, study, or drug are known.

PATIENT'S NAME _____

SIGNED BY: _____
(Patient or Legal Guardian)

WITNESS: _____

I, the undersigned, herewith affirm that I have explained the above to Mr. (Mrs.) (Miss) _____ and I am willing to answer further inquiries.

_____ M D DATE _____

1179627

Form 1913 -74-

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE:

TO:

FROM: R.B. Aronson, Ph.D.

SUBJECT: CIRC Proposal 10 C

In compliance with recent FDA and HEW notices requiring periodic reviews of clinical research projects, your CIRC proposal, number____ is scheduled for review soon. Please indicate at the bottom of the page if this proposal should be continuing or placed on the inactive list.

This proposal was last reviewed and approved by the Committee on_____ 19____. Do you wish to make any substantive changes in your proposal? YES see attached MEMO — dated 9/14

Have you noticed any adverse effects during the experimental program which have not already been reported to the Department Chairman's Office? NO. Please include the nature and frequency of such effects.

_____

_____

_____

Approximately how many patients have been submitted to the experimental regime since the last approval? 9

The Sponsoring Physician on this proposal is ATKINS. Has there been a change of Sponsoring Physician or Responsible Investigators? NO

_____

If you have obtained IND numbers from the FDA in connection with this proposal please list on a separate sheet the compounds and corresponding IND numbers, and attach. IND 4687

Please attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given above), since the last CIRC approval date.

Please add any additional information which may be of use to the Committee in its diliberations. Include a copy of the Patient Consent Form now in use for this study.

CIRC PROPOSAL NUMBER _____ IS: Continuing ☐

Inactive ☐

Signed X Harold L. Atkins 9-13-72

Date

Please return this completed form to Dr. R.B. Aronson as soon as possible.

1179628

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 14 September 1972

TO: CIRC

FROM: S. H. Cohn, et al

SUBJECT: REACTIVATION OF CIRC 10C (IND 4687)

It is requested that CIRC 10C, "Effect of Fluorine on osteoporosis" be reactivated. The dose of sodium fluoride (20 mg F/day) administered is the same but the length of the study will be changed from 6 weeks to one year. In addition the patients will receive calcium supplementation of their diet (1 g/day).

The lack of significant effect in the original study is felt to be due to the short period of the study and the lack of calcium supplementation of the diet.

1179629

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: MAY 25, 1971

TO: DR. COHN

FROM: R.B. Aronson, Ph.D.

SUBJECT: CIRC Proposal 10C

In compliance with recent FDA and HEW notices requiring periodic reviews of clinical research projects, your CIRC proposal, number 10C is scheduled for review soon. Please indicate at the bottom of the page if this proposal should be continuing or placed on the inactive list.

This proposal was last reviewed and approved by the Committee on Sept. 24, 1969. Do you wish to make any substantive changes in your proposal? _____

Have you noticed any adverse effects during the experimental program which have not already been reported to the Department Chairman's Office? No. Please include the nature and frequency of such effects.

_____

_____

_____

Approximately how many patients have been submitted to the experimental regime since the last approval? 10

The Sponsoring Physician on this proposal is Dr N. Atkins. Has there been a change of Sponsoring Physician or Responsible Investigators? No

_____

If you have obtained IND numbers from the FDA in connection with this proposal please list on a separate sheet the compounds and corresponding IND numbers, and attach. IND - 4687 - (Sodium Fluoride)

Please attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given above), since the last CIRC approval date.

Please add any additional information which may be of use to the Committee in its diliberations. Include a copy of the Patient Consent Form now in use for this study.

CIRC PROPOSAL NUMBER 10C IS: Continuing [X]

Inactive [ ]

Signed Stanton H. Cohn 5-25-71
Date

Please return this completed form to Dr. R.B. Aronson as soon as possible.

1179630

The Committee on Clinical Investigations and Use of Radioisotopes hereby approves the program with the following title:

Clinical tracer study using Sodium Fluoride on patients with Senile Osteoporosis.

CIRC # 10 (C) has been assigned to this program.

Kanti Rai, M.D., Acting Chairman

Robert Love, M.D.

James Robertson, M. D.

Date: 9-24-69

Place: Medical Research Center
Brookhaven National Laboratory
Upton, New York 11973

Committee on Clinical Investigations and Uses of Radioisotopes

Approval Recommended _____ Date _____

Disapproval _____ Date _____

E. P. Cronkite, M. D.
Chairman, Medical Department

Date

1179631

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: September 24, 1969

TO: Dr. S. H. Cohn

FROM: Dr. K. R. Rai

SUBJECT: Use of Fluoride in Ca^{47} Tracer Studies

The Committee on Clinical Investigations and Use of Radioisotopes in its meeting of 9/24/69 has unanimously approved your proposed addendum CIRC 10(c), subject to the following reservation:

> "In the case of those patients, who participate in ~~repeated~~ studies involving multiple doses of radioisotopes and/or radiation due to neutron activation, the cumulative radiation dose will remain within the permissible levels as established by the AEC guidelines".

Kindly let me know if you are willing to incorporate this in your addendum 10(c) - so that the appropriate recommendation of the Committee may be sent to the Chairman of the Medical Department.

/bn

cc: Dr. Love
Dr. Robertson

1179632

Minutes of Committee on Clinical Investigations and Use of Radioisotopes

September 24, 1969

Meeting came to order at 1405 hours with Drs. K. R. Rai, R. A. Love and J. S. Robertson being present.

The agenda as previously circulated was the proposed addendum (c) to CIRC #10 of Dr. Stanton Cohn. Dr. Rai informed the members that Dr. H. L. Atkins and Dr. S. H. Cohn, members of the Committee, were excused from attending this meeting as they are investigators of the proposal under consideration. Among the other members, Dr. H. A. Johnson was on jury duty and Drs. L. K. Dahl and D. C. Borg were on vacation.

After some discussion, the details of which follow, the Committee unanimously approved the proposed addendum with one reservation.

Dr. Love pointed out that according to the stipulation in the memo from Drs. Cohn et al of 2/20/68, (vide last para.) the combined effects of NaF and Ca supplementation will also be studied on a group of patients. Will these patients be the same as the ones who will have been studied with either NaF or Ca alone or they will be different individuals? The total radiation dose to an individual must be born in mind and the permissible limits must not be exceeded.

In the same context, Dr. Rai felt that considering the proposal to include the same patients in the study by neutron activation (approved as CIRC #36) as stated by Dr. Cohn in his memo of 9/16/69, the investigators should ensure that the total radiation dose to an individual patient (participating in the combined studies) is reviewed at appropriate times.

Dr. Robertson agreed with these reservations. The following reservation was then proposed:

> "In the case of those patients who participate in repeated studies ~~or multiple studies~~ involving several doses of radioisotopes and/or radiation due to neutron activation, the cumulative radiation dose must remain within the permissible levels as established by the AEC guidelines".

It was unanimously decided that the above noted reservation be communicated to Dr. Cohn and the approval to the proposed addendum be subject to Dr. Cohn's acceptance of the reservation.

Dr. Robertson observed that Dr. Cohn, in his memo of 9/16/69 has reduced the daily fluoride dose to 20 mg/day from the earlier suggested dose of 60 mg. Dr. Robertson wondered if the toxicity of fluoride has been adequately looked into. Dr. Rai said he had seen the references 3, 4 and 5 (of memo dated 2/20/68 from Cohn et al) and is satisfied that fluoride is not as toxic as the old literature would have us believe.

Actually, all the recently published data suggest that fluoride is not only relatively nontoxic and safe but has very promising potential in geriatric medicine. The doses proposed to be given in the studies under consideration were definitely safe according to Dr. Rai's review.

Dr. Love pointed out that Dr. Cohn has addressed both of his memos (9/16/69 and 2/20/68) to Clinical Radioisotope Committee. For the sake of proper records, the correct name of this committee should be used.

The Committee signed the front page of the proposed addendum 10(c) with the proviso that the above noted reservation be satisfied by Dr. Cohn prior to communicating approval of the Committee to him.

The meeting was adjourned at 1430 hours.

Respectfully submitted,

Kanti R. Rai

Kanti R. Rai, M.D.

cc: Dr. Love
Dr. Robertson

BROOKHAVEN NATIONAL LABORATORY

26 Feb. 1968

Memo to Cohn Dept.

Stan,

I really don't see how one can give fluorides to people without an IND - FDA.

Please discuss with CIRC

E

EUGENE P. CRONKITE, M.D.
Chairman, Medical Department
from Brookhaven National Laboratory Dept.
Upton, New York 11973

FORM NO. 112-A
UPTON, N. Y. 2-57

1179635

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: Feb. 20, 1968

TO: Clinical Isotope Committee

FROM: Drs. S.H. Cohn, W. Hauser and H.L. Atkir

SUBJECT: Approval for clinical tracer study

Permission is requested to perform an addition to the study on osteoporosis described in memo of February 3, 1967 and in H-64 protocol.

The general protocol will be exactly as described with the exception that sodium fluoride will be fed in place of Ca supplements.

A number of studies have indicated that fluoride at appropriate levels has a beneficial effect on the calcium metabolism of osteoporotic patients. Relatively low doses of fluoride act to depress the resorption of bone. The overall results suggest that F has a profound effect on calcium balance manifested by a decreased rate of urinary Ca excretion. The object of this study is to quantify the underlying kinetic effect of F in osteoporotic patients and to measure subtle beneficial changes.

Sodium fluoride administered orally in divided doses of 60 mg/day of F for 14 weeks was shown to have no untoward effects (2). Black, Kleiner and Bolker also found no evidence of toxicity in 60 human subjects treated for as long as 6 months with an average daily dose of 320 mg NaF (2.4 mg F/kg/day) for a 60-kg subject (4). Rich (3) reported no evidence of nonskeletal effect (chemical, clinical or roentgenographic) at 1 mg F/kg/day. In one patient epigastric pain was initially observed. This was ameliorated by measures which reduce gastric acidity and by the use of enteric coated tables. There was pain in joints observed in three patients which could be ascribed to the exacerbation of existing degenerative arthritis symptoms by the NaF, but this is not clear. There were no other symptoms and no biochemical evidence of toxic effects in any patients. Very high levels of fluoride in man can lead to fluorosis with excessive bone formation (6,7). Levels of 4000-5000 ppm in bone have been shown to have deleterious effects on bone (6). The toxicity of F is largely a function of a high dose rate and an extended duration of the intake of from 5-20 years (6).

The proposal for the present study is to administer NaF to 8 osteoporotic patients at the dose described by Rich, 60 mg/day for 6 weeks maximum. The tracer kinetic study with ^{47}Ca will be performed before and after the F feeding.

Following this study and pending successful results, the combined effects of NaF and Ca supplementation will be studied on a group of osteoporotic patients. The results of the high Ca diet study indicates a beneficial effect in terms of Ca deposited in bone. The mechanism of F action appears to differ from that of Ca supplementation, and therefore the effects of the combined treatment should be additive.

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: Sept. 16, 1969

TO: Clinical Radioisotope Committee

FROM: Dr. S.H. Cohn

SUBJECT: Approval for clinical tracer study

We would like to initiate this study as originally submitted to the Committee on February 20, 1968. At that time it was requested that we apply for FDA approval. The FDA application, as well as the receipt of our application by the FDA, is attached.

More recent studies have indicated that the desired effects can be obtained with lower administered doses of NaF. Accordingly, we will reduce the daily fluoride dose to 20 mg/day. The other innovation in the schedule is to incorporate neutron activation analysis for calcium in the protocol. This later procedure has already been approved of by the Clinical Investigation Committee (CIRC 36) for patients with advanced senile osteoporosis.

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 9/21/72

TO: CIRC 10C file

FROM: S.H. Cohn SHC

SUBJECT:

This is to formally confirm the incorporation of the Committees proposed addendum to CIRC 10C: "In the case of those patients, who participate in studies involving multiple doses of radioisotopes and/or radiation due to neutron activation, the cumulative radiation dose will remain within the permissible levels as established by the AEC guidelines" as requested in memorandum of Dr. K.R. Rai, 9/24/69.

REFERENCES

1. D. M. Hegsted. Beneficial and detrimental effects of fluoride in the environment. Proc. Ann. Conf. on Trace Elements in Environmental Health, Univ. Missouri, 1967.

2. G. Rich and J. Ensinck. Effect of sodium fluoride on calcium metabolism in human beings. Nature 191, 185, 1961.

3. C. Rich, J. Ensinck, and P. J. Ivanovich. The effects of sodium fluoride on calcium metabolism of subjects with metabolic bone diseases. J. Clin. Invest. 43, 545, 1964.

4. M. M. Black, I. S. Kleiner, and H. Bolker. The toxicity of sodium fluoride in man. N. Y. State J. Med. 49, 1187, 1949.

5. D. S. Bernstein, N. Sadowsky, D. M. Hegsted, C. D. Guri, and F. J. Stare. Prevalence of osteoporosis in high and low fluoride areas in North Dakota. J.A.M.A. 198, 499, 1966.

6. H. C. Hodges and F. A. Smith. Fluorine Chemistry, Vol. IV., J. H. Simons, Ed., Academic Press, New York City, 1965, p. 52.