THE CHEMISTRY OF UROSELECTAN

ARTHUR BINZ

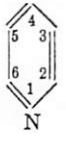
Professor of Chemistry at the Landwirtschaftliche Hochschule, Berlin

Mr. President! and Members of the American Urological Association!

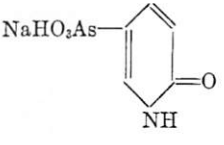
I consider it a great honour to be afforded the opportunity today of appearing at your meeting and presenting a short paper on the Chemistry of Uroselectan. I wish to thank you sincerely for this privilege you have permitted.

In the synthesis of salvarsan chemical efforts were confined to one class of chemical compounds, the benzene series. The therapeutic effect of the salvarsan-group depends principally on the arsenic element, which is attached to the *carbo*cyclic benzene-nucleus. This benzene-nucleus itself has little or no therapeutic effect. The quinine group however depends for its therapeutic efficiency on the *hetero*cyclical nuclei themselves and not upon any element like arsenic attached to them.

It was my idea in 1921 to attach arsenic or other elements such as iodine to heterocyclical nuclei and possibly thereby intensify therapeutic efficiency in the treatment of syphilis.



I



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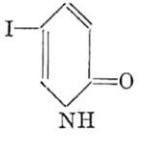

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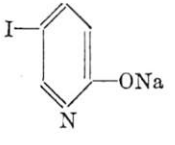
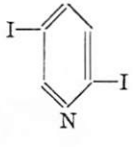


IV

Selectan 51% I



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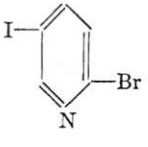

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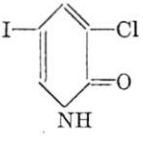

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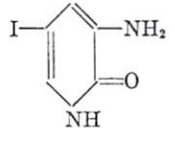

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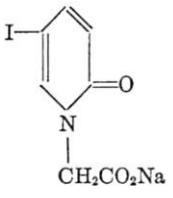
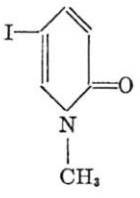


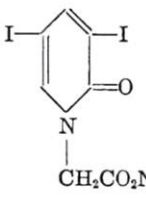
IX

Uroselectan
42% I



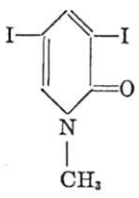
X

Selectan
neutral
54% I



XI

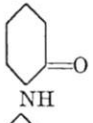
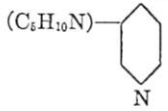
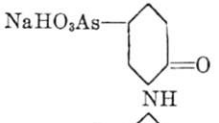
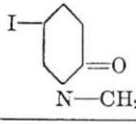
59% I



XII

70% I

	PERCENTAGE OF IODINE	DOSIS TOXICA IN GRAMS IODINE PER 1-KGM. RAT
Uroselectan	42.1	3.27
Sodium iodide	84.7	0.6–1.2
Yatren	28.0	0.07
Alival	62.8	0.037

		DOSIS TOXICA, MGM. PER GRAM RAT
Pyridine		1.0
2-Pyridone		1.5
Nicotin		0.01
Sodium salt of 2-Pyridon-5-arsinic acid		6.0
Uroselectan		8.0

My assistant Dr. *Räth* and I chose the simplest heterocyclical nucleus, the pyridine (I), and transformed it into the sodium salt

of 2-pyridone-5-arsinic acid (II) and also into the corresponding 5-iodine-2-pyridone (III), both of which proved to be bactericidal; and compound IV, which is the sodium salt of compound III, we found to be particularly efficacious in the treatment of streptococcic mastitis of cows. In 1927 this compound IV was introduced in veterinary medicine under the name *Selectan.*

Work of this kind always necessitates more endeavour, for it should be the duty of the original workers to extend the field of usefulness as far as possible. Therefore Dr. Räth, whom I trusted with this particular part of our work, synthetised 73 iodine-pyridine-compounds, some of which are shown here, for instance formula V and VI, where the ONa-group of selectan is replaced by halogens; or formula VII and VIII, where others substituents are introduced next to oxygen; or thirdly formulas IX to XII where various substituents are attached to nitrogen.

The two factors, which might improve the efficiency of selectan, are higher percentage of iodine (for instance in V, XI and XII) or increased solubility. Selectan itself is only 4 per cent soluble; compound X, which contains 54 per cent iodine, and which we named *Selectan neutral,* is 10 per cent soluble. An interesting point is, that compound IX, which was later called *Uroselectan,* contains only 42 per cent iodine but is 35 per cent soluble. Uroselectan was synthetised in 1927.

Professor *Lichtwitz* was kind enough in November, 1928, to investigate selectan neutral in septical human cases and, I understand, observed some success, but he also observed that selectan neutral had a most remarkable other effect which concerned the visualisation of the urinary tract. Dr. *Hryntschak* of Vienna in October, 1927, had also been working with selectan-compounds among which was the later so called uroselectan, but without clinical success.

In March, 1929, I discussed matters with Prof. Lichtwitz and Dr. *Swick.* The clinical work was continued under Prof. *v. Lichtenbergs* direction in Berlin, and with him, before his voyage to America in June, 1929, we reviewed the chemical and biological qualities our various iodine-products would have to have in order to be clinically applicable. Prof. von Lichtenberg selected the

cases for investigation and appointed Dr. *Swick* to clinically try out the preparations that I would give him.

Prof. von Lichtenberg and I had agreed to consider on the one hand the substances with a maximum of iodine and on the other hand those with a maximum of solubility. Therefore, as selectan neutral, although 10 per cent soluble, was not sufficiently soluble to afford the possibility of administering enough iodine for visualisation of the urinary tract, I suggested to try two substances with a high percentage of iodine (XI with 59 per cent and XII with 70 per cent). Although the second iodine-atome present in these molecules considerably diminishes solubility, we thought the organism might eliminate the necessary amount of iodine for visualization of the kidneys. The clinical result was, as I understand, that the drugs were eliminated for the most part through the intestines and not sufficiently through the kidneys. Then, according to the program worked out with Prof. v. Lichtenberg, solubility was taken as the leading rôle and I fixed upon substance IX, and although it did not recommend itself by containing a maximum of iodine, I knew it to surpass all the others in solubility and tolerability from investigations made two years previously in my laboratory.

Substance Nr. IX brought us the long sought effect and on Prof. v. Lichtenbergs suggestion we named it uroselectan.

The relative harmlessness of uroselectan is unique not only among iodine-compounds but also among pyridine-compounds. This may be illustrated by two tables, which show the toxicity in rats.

The figures indicate that iodine in the form of uroselectan is about 4 times less toxic than the equal amount of iodine in the form of sodium iodide and about 49 times less toxic than iodine in the form of yatren and about 88 times less toxic than in the form of alival.

The initial substances pyridine and 2-pyridone are fairly tolerable. The toxic substance nicotine contains the group $C_5H_{10}N$ in the same relative position as the 2-pyridone-5-arsenic acid contains arsenic and as uroselectan contains iodine. But contrary to what we might expect, arsenic in this position does not

lead to an increase in toxicity, but to an increase in tolerability; and the same is the case with the similarly placed iodine in connection with the acetic acid radical fixed to the nitrogen of uroselectan.

Concerning stability it is interesting to compare the uroselectan-molecule to that of 2-pyridone-5-arsenic-acid. One may heat this arsenic-compound with water to a temperature of 150 C. for eight hours without the arsenic-radical being split off from the molecule. Only a slight decomposition takes place at 170°. But if the nitrogen in this nucleus is replaced by carbon, so that we have a benzene-derivative, then the arsenic radical splits off readily at boiling temperature within half an hour. Nitrogen being present at this point in the uroselectan-molecule may explain the fact that iodine is firmly bound to the molecule and is not split off under ordinary chemical procedures.

It has been very pleasant for me to visit you in America and to have the privilege of appearing at your meeting. I have been more than happy to coöperate with the medical profession and it is a point of gratification to me that the results of chemical investigations of some years ago might prove in your hands to be of medical value.

168 Kaiserallee,
Wilmersdorf, Berlin

DISCUSSION

Dr. JOHN A. KILLIAN (New York City): In the discussion of Dr. Binz's paper, I am going to report a few observations upon the secretion of uroselectan and its influence upon metabolism. The first slide, please.

(Slide) In this first slide we have a few typical cases of a large series (15) showing the relation of the concentration of uroselectan in the blood to the rate of secretion in the urine and the volume of urine voided. In the first case, although there was a unilateral hydronephrosis, there was apparently normal renal function according to all laboratory tests, and during the period of twenty-four hours 90 per cent of the uroselectan has been secreted. In two instances, there was evidence of poor renal function and a small fraction of the uroselectan has been secreted. It is

EXCRETION OF UROSELECTAN IN URINE				
PATIENT	UROSELECTAN IN BLOOD MG. PER 100 ML.	UROSELECTAN IN URINE GM. IN 24 HRS.	URINE VOLUME IN 24 HRS.	PERCENT EXCRETED	DIAGNOSIS
L.K.	70	37.2	1620	93	UNILATERAL HYDRONEPHROSIS
D.L.	265	23.2	1240	50	PROSTATECTOMY PREVIOUSLY
C.F.	93	26.5	1640	66	TUBERCULOUS EPIDIDYMITIS AND ORCHITIS
F.C.	93	66	4455	28	TUMOR OF BLADDER
B.L.	151	66	652	44	CHRONIC PYELITIS
C.K.	10	4.7	1356	11	PERINEPHRITIC ABSCESS
F.C.	317	30.5	1565	50	PROSTATIC HYPERTROPHY RETENTION CATHETER
A.N.	260	11.5	1404	28	BILATERAL ROTATION OF KIDNEYS

FIG. 1

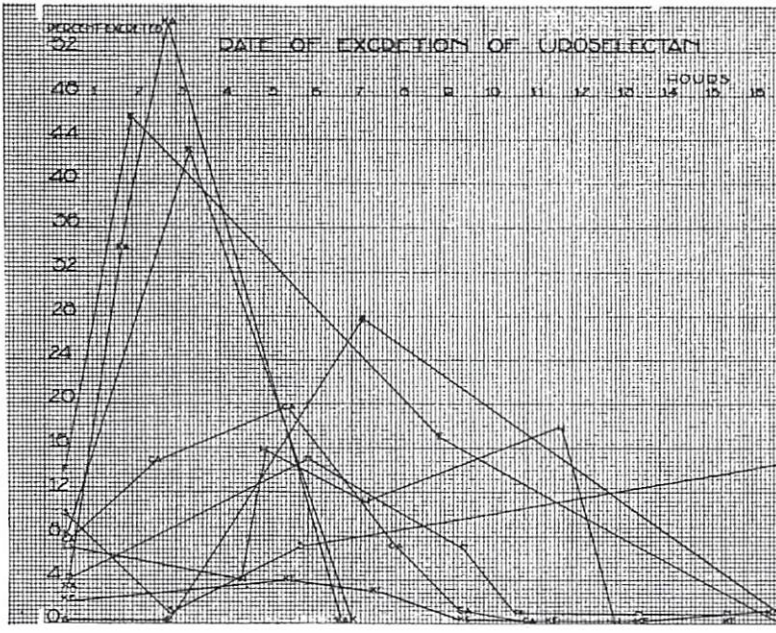


FIG. 2

interesting to note that the percentage of the dye excreted bears no definite relation to the concentration in the blood after an interval of thirty minutes following the injection. It is also interesting to note that these patients secreted a large volume of urine. After uroselectan, the volume of urine secreted was from two to three times the volume secreted during twenty-four hours preceding the administration of the drug.

(Slide) This slide presents graphically the rate of excretion of uroselectan from thirty minutes to twenty-four hours after the administration. The first three curves reported here represent the normal excretion of uroselectan with normal renal function. There are two curves showing the low rate of excretion of the uroselectan with poor renal function during a period of twenty-four hours. The curve marked *S* is an extraordinarily interesting one, inasmuch as it shows a marked fluctuation in the concentration of the uroselectan in the urine for a period of twenty-four hours. In films taken of the urinary tract of this case during a period of five hours after the injection of the dye, there was a poor visualization of the urinary tract. It is interesting to note that the maximum excretion here occurred seventeen hours after the administration of uroselectan. I believe these figures indicate the necessity of the elaboration of a rapid clinical method for the determination of the concentration of uroselectan in the urine, which can be utilized in the room where cystoscopy is being done. Professor Binz tells me that at the present time they are working on such a method.

(Slide) It occurred to us that the administration of a large dose of a pyridine derivative in a large volume of solution might have some effect upon cardiac function. In order to study that question we have utilized the method of determining the oxygen unsaturation of the blood, first described by Lundsgaard in 1918, and in our experience has proven to be the most satisfactory method of determining cardiac function. It simply consists in determining the oxygen capacity of the blood represented by the first column and the oxygen content of the blood by the second column. The difference between these two is the oxygen unsaturation of the blood, which in normal venous blood should be about five to eight volumes per cent and represents the amount of oxygen removed from the arterial blood by the tissues supplied by that blood. You note in this chart in a cardiac decompensation the oxygen unsaturation of the blood is markedly increased, but in compensated heart lesions there is no change from normal in the oxygen unsaturation.

(Slide) Here we have compared the hemoglobin by oxygen capacity and oxygen content before and after uroselectan. The observations

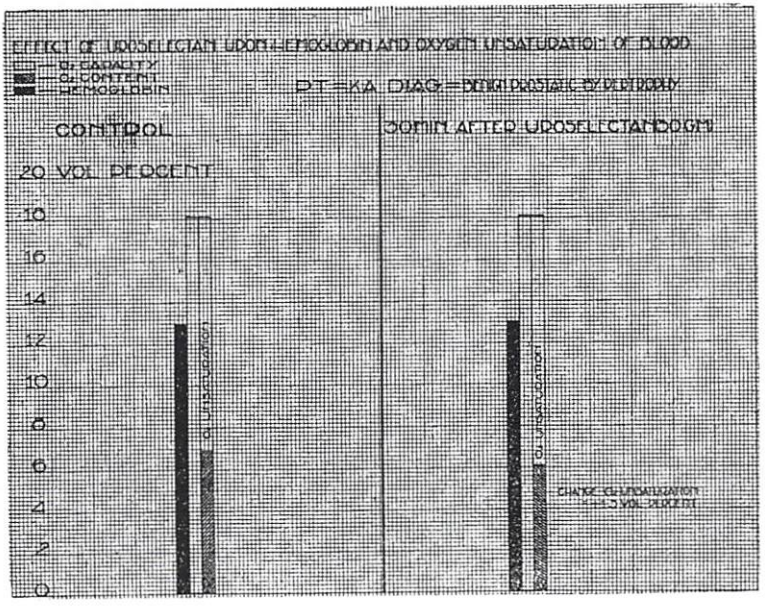

EFFECT OF UROSELECTAN UPON HEMOGLOBIN AND OXYGEN UNSATURATION OF BLOOD
O2 CAPACITY
O2 CONTENT
HEMOGLOBIN
DT = KA DIAG = BENIGN PROSTATIC HYPERTROPHY
CONTROL
30MIN AFTER UROSELECTAN (0.06 GM)
20 VOL PERCENT
18
16
14
12
10
8
6
4
2
0
O2 UNSATURATION
O2 UNSATURATION
CHANGE IN O2 UNSATURATION
+ 5.3 VOL PERCENT

FIG. 3

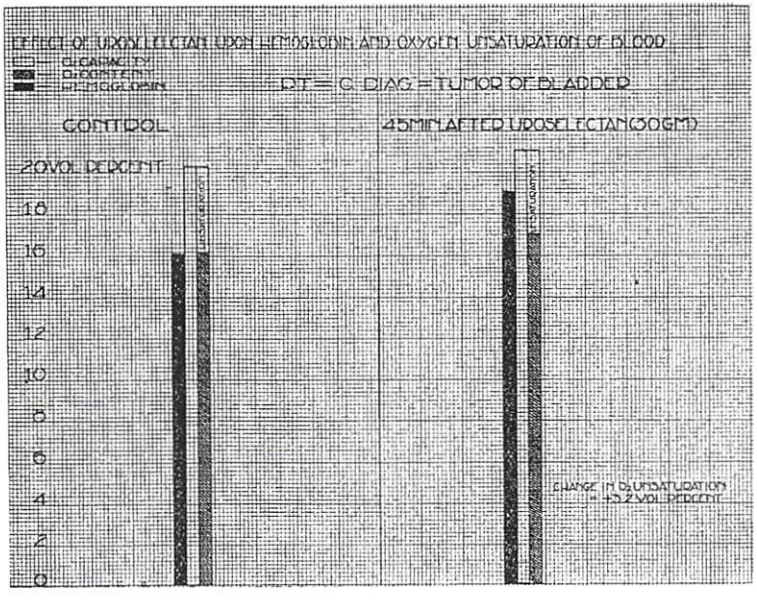

EFFECT OF UROSELECTAN UPON HEMOGLOBIN AND OXYGEN UNSATURATION OF BLOOD
O2 CAPACITY
O2 CONTENT
HEMOGLOBIN
DT = C DIAG = TUMOR OF BLADDER
CONTROL
45MIN AFTER UROSELECTAN (0.06 GM)
20 VOL PERCENT
18
16
14
12
10
8
6
4
2
0
O2 UNSATURATION
O2 UNSATURATION
CHANGE IN O2 UNSATURATION
+ 5.2 VOL PERCENT

FIG. 4

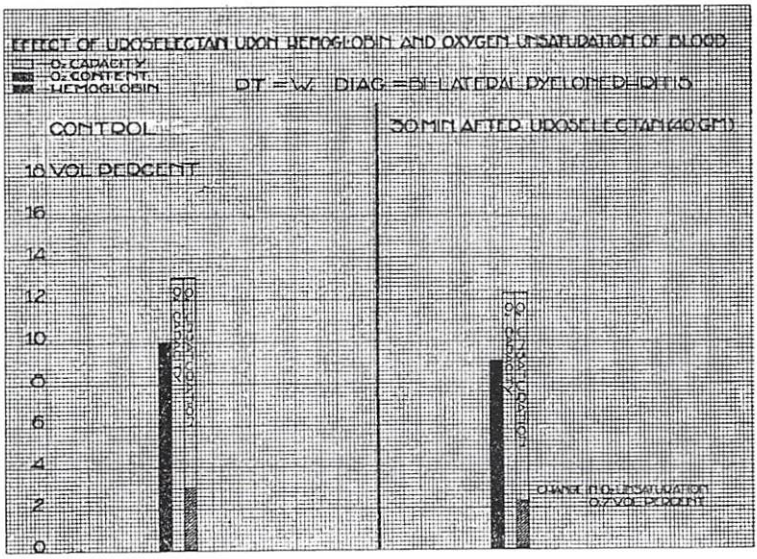

EFFECT OF UROSELECTAN UPON HEMOGLOBIN AND OXYGEN UNSATURATION OF BLOOD
O2 CAPACITY
O2 CONTENT
HEMOGLOBIN
DT = W. DIAG = BILATERAL PYELONEPHRITIS
CONTROL
30 MIN AFTER UROSELECTAN (40 GM)
20 VOL PERCENT
16
14
12
10
8
6
4
2
0
O2 UNSATURATION
CHANGE IN O2 UNSATURATION
O2 VOL PERCENT

FIG. 5

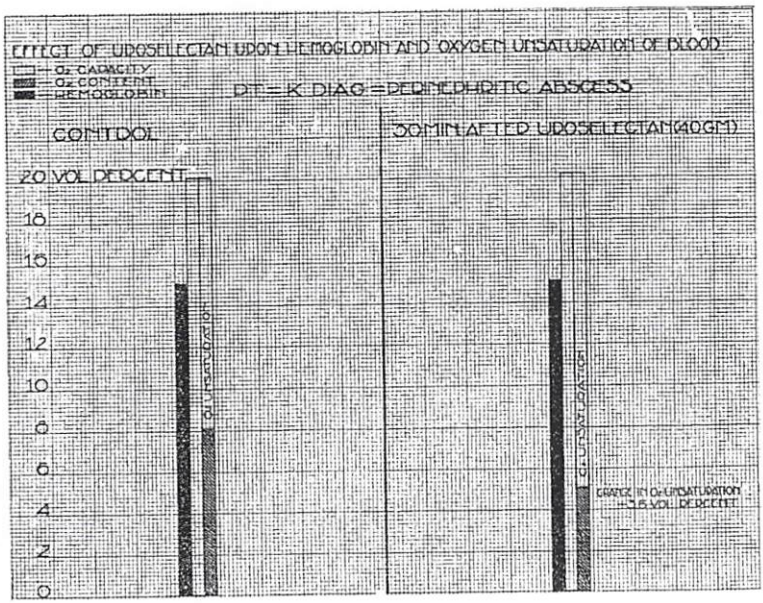

EFFECT OF UROSELECTAN UPON HEMOGLOBIN AND OXYGEN UNSATURATION OF BLOOD
O2 CAPACITY
O2 CONTENT
HEMOGLOBIN
DT = K DIAG = PERINEPHRITIC ABSCESS
CONTROL
30 MIN AFTER UROSELECTAN (40 GM)
20 VOL PERCENT
18
16
14
12
10
8
6
4
2
0
O2 UNSATURATION
CHANGE IN O2 UNSATURATION
+3.6 VOL PERCENT

FIG. 6

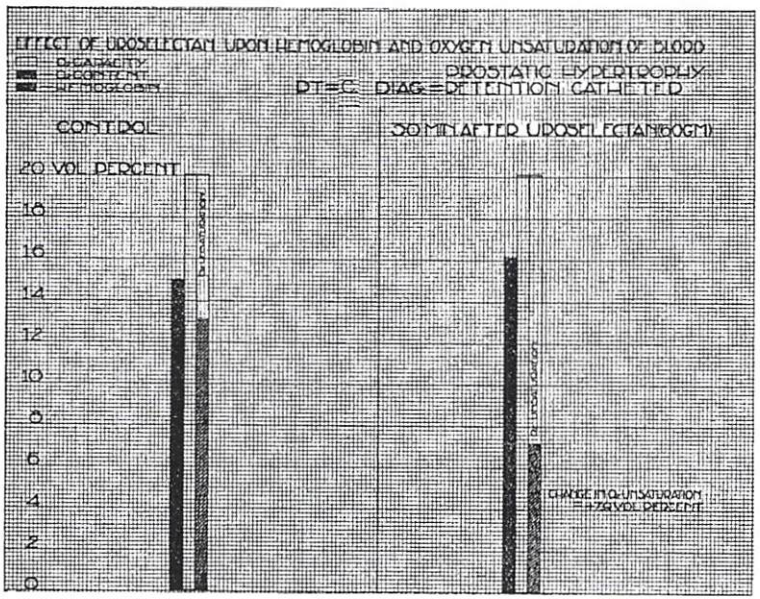

EFFECT OF UROSELECTAN UPON HEMOGLOBIN AND OXYGEN UNSATURATION OF BLOOD
O2 CAPACITY
O2 CONTENT
HEMOGLOBIN
PROSTATIC HYPERTROPHY
DT=C DIAG=DETENTION CATHETER
CONTROL
30 MIN AFTER UROSELECTAN (100 GM)
20 VOL PERCENT
18
16
14
12
10
8
6
4
2
0
O2 CAPACITY
O2 UNSATURATION
CHANGE IN O2 UNSATURATION = 7.2 VOL PERCENT

FIG. 7

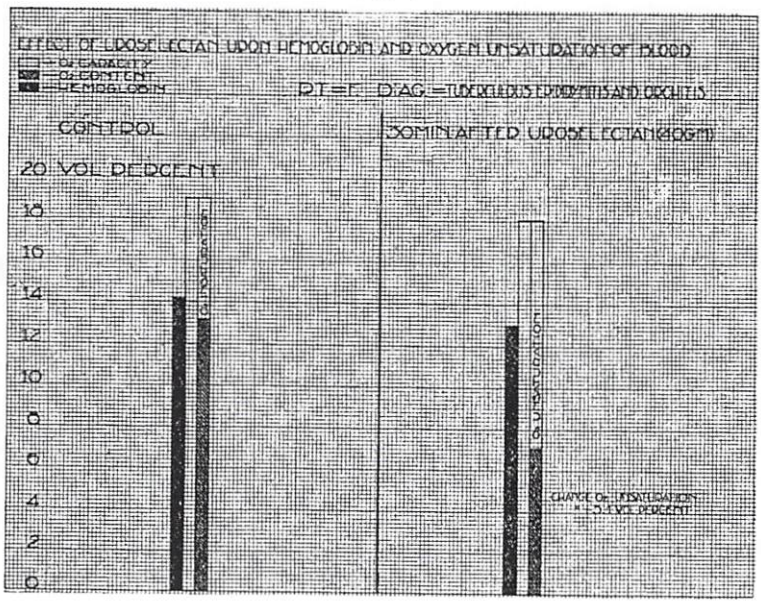

EFFECT OF UROSELECTAN UPON HEMOGLOBIN AND OXYGEN UNSATURATION OF BLOOD
O2 CAPACITY
O2 CONTENT
HEMOGLOBIN
DT=C DIAG=TUBERCULOSIS PROSTATITIS AND ORCHITIS
CONTROL
30 MIN AFTER UROSELECTAN (100 GM)
20 VOL PERCENT
18
16
14
12
10
8
6
4
2
0
O2 CAPACITY
O2 UNSATURATION
CHANGE IN O2 UNSATURATION = 5.4 VOL PERCENT

FIG. 8

after uroselectan were made thirty minutes after the injection. The black column represents the hemoglobin, the white column, the oxygen capacity, the shaded column, the oxygen content and the difference between the oxygen content and capacity is the oxygen unsaturation. You will note there is an increase in oxygen unsaturation of the blood after the uroselectan, but there is relatively less change in hemoglobin concentration.

(Slide) This patient showed a marked reaction to uroselectan which manifested itself clinically as a development of a pronounced deep cherry red color throughout the entire body and profuse sweating. It is interesting to note that after the uroselectan there is an increase in the hemoglobin of the blood, probably due to a concentration of the peripheral blood. There is also a decrease of 7.9 volumes per cent in oxygen unsaturation.

(Slide) This also shows an increase in hemoglobin of the blood, probably due to concentration of the peripheral blood by the removal of fluid.

(Slide) This was a case which showed some impairment of cardiac function before the administration of uroselectan. You note the oxygen unsaturation is much above the normal. Here it is about 12 volumes per cent; following the administration of the uroselectan, there is an increase in oxygen unsaturation of only 1.3 volumes per cent. In other words, the administration of uroselectan in this case with cardiac impairment did not emphasize or increase the cardiac impairment.

(Slide) This also shows the effect of uroselectan upon the oxygen unsaturation of the blood in a case of cardiac impairment. Here again we have only a slight increase in oxygen unsaturation.

(Slide) We have compared here the CO_2 content of the blood before and after uroselectan. The content is represented by the white column before the administration of uroselectan and afterwards by the shaded column. The black column represents the change in CO_2 content. It is interesting to note that in 2 cases, 1 and 4, there was an increase in CO_2 content of approximately 1 volume per cent. In the other cases, there is a decrease in CO_2 content, from about 5 to 7 volumes per cent.

(Slide) Theoretically if uroselectan has any effect upon cardiac function, there should be a definite relation between the change in CO_2 content and the oxygen unsaturation of the blood. In other words, as the oxygen unsaturation of the blood is increased, there should also be an increase in CO_2 content, not a decrease, because impairment of cardiac function would diminish the aeration of the blood in the lungs. In other words, our curve for the CO_2 content in relation to oxygen unsatu-

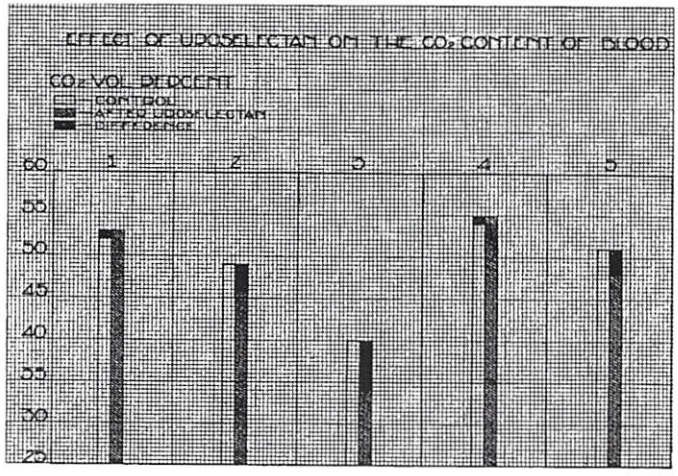

EFFECT OF UROSELECTAN ON THE CO2 CONTENT OF BLOOD
CO2 VOL PER CENT
CONTROL
AFTER UROSELECTAN
DIFFERENCE
60
55
50
45
40
35
30
25
1
2
3
4
5

FIG. 9

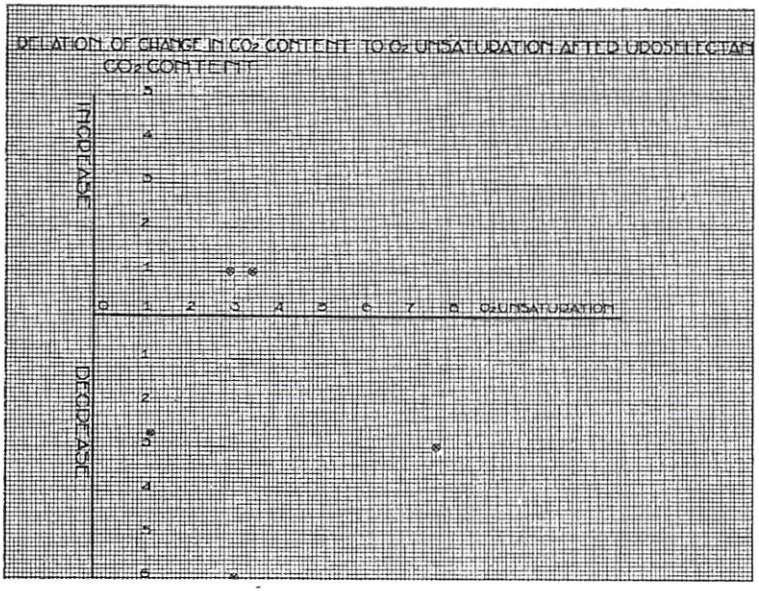

RELATION OF CHANGE IN CO2 CONTENT TO O2 UNSATURATION AFTER UROSELECTAN
CO2 CONTENT
INCREASE
DECREASE
O2 UNSATURATION
0
1
2
3
4
5
6
7
8

FIG. 10

ration should follow a diagonal course, of 45°. You note where we have plotted the CO_2 content, it changed without relation to oxygen unsaturation. It does not follow the expected curve. In some cases we have a decrease in CO_2 content where we would expect an increase. It is very probable, I believe, that a change in CO_2 content in the blood may be due to an increase in body temperature, with an increased rate of ventilation of CO_2 from the venous blood. On the other hand the changes in oxygen unsaturation and CO_2 content of the blood may be due to a greater removal of gases from the peripheral blood or blood in the abdominal viscera, consequent to arteriole and capillary dilatation.

Dr. P. B. HUGHES (Carbondale, Pa.): Mr. President, may I make a preliminary report concerning the mechanism of uroselectan excretion from the kidney? It was interesting to us to determine whether it was excreted principally through the glomerulus or tubules. Investigating with the kidneys of frogs after intravenous injection of uroselectan and doing the various procedures, in all our experiments, after checking glomerular fluid for half an hour, we have detected an appreciable amount of iodine in the glomerular fluid. We detected fourteen-millionths of a gram of uroselectan from one glomerulus after a half hour of checking, following intravenous injection of 0.75 of a gram.

I wish to make this as a preliminary report that uroselectan is easily eliminated from the kidney principally through the glomeruli.