female form to be the basic or neuter, and the male differentiation to occur only in the presence of functioning testes during development of the embryo. Graham, in his experimental study in cats, has pointed out that sex chromatin can be recognized in the early embryo before the gonads have appeared, and therefore the sex is genetically determined and does not depend upon the hormonal status of the individual. Hoffenberg and Jackson have explained the varieties of gonadal dysgenesis and the various forms of human intersex by postulating three closely connected genes situated on the same chromosome. These authors have postulated one gene for infantilism or intrauterine hypogonadism—called "I"; one gene for shortness of stature, "S"; and one gene-complex for various anomalies of vegetative system called "A." According to them, the infantilism in gonadal dysgenesis results from very early failure of the developing gonad (their factor I), with consequent feminization of genital tract and body form. If gonadal dysgenesis occurs at a later stage of the male embryonic development, partial development along masculine lines will already have taken place. Further development of the genital tract will be of the female type, and thus "male pseudohermaphroditism" will result. This is equivalent to their "I" factor coming into operation at a slightly later stage. They conclude thus: "I" alone (slightly later in genetic male)—male pseudohermaphroditism; "I" (slightly later in genetic male) + S + A—male pseudohermaphroditism with short stature and anomalies.

The observations of Jost and Graham have led to the adoption of the term "gonadal dysgenesis" in preference to "ovarian agenesis." It also suggests that the Goldberg–Maxwell syndrome is, in fact, a variety of gonadal dysgenesis, where genetic development has failed in its attempt to produce a normally functioning testis and therefore the basic female pattern has continued. In this syndrome the failure to develop has probably occurred at a very early stage of development of the embryo, with the emergence of a complete feminine form and none of the male features. We can therefore say that the Goldberg–Maxwell syndrome is the earliest form of male pseudohermaphroditism.

Summary

The syndrome of Goldberg and Maxwell occurring in three sisters has been described.

The various features of the syndrome have been surveyed in detail.

The genetic aspects of the syndrome have been discussed in the light of modern work, and a hypothesis is produced to account for the syndrome.

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AN ERYTHROPOIETIC FACTOR PRODUCED IN THE KIDNEY

PRELIMINARY REPORT

BY

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A systematic study has been made of the response in mice to *x*-irradiation of the kidneys. The exteriorized kidneys were exposed to a single *x*-ray irradiation. The doses ranged between 100 and 18,000 r. By irradiation of the kidneys in mice a condition was produced resembling the essential features of glomerulonephritis in man with increasing nitrogen accumulation in the blood, anaemia, acidosis, oedema, hypertonia with hypertrophy of the heart, atrophy and granulation of the kidneys, albuminuria, haematuria, cast formation, decreased concentration of the urine to isosthenuria, and final collapse in a uraemic condition.

Experimental Findings

After 8,000 to 12,000 r increased blood pressure was observed in 10 days, whereas after 1,000 r about 8–12 months was necessary for this development. After unilateral nephrectomy and irradiation of the remaining kidney with 500 r the blood urea level increased in the course of five months. With the same procedure, and using 8,000 r, a rise in blood urea was observed after five days.

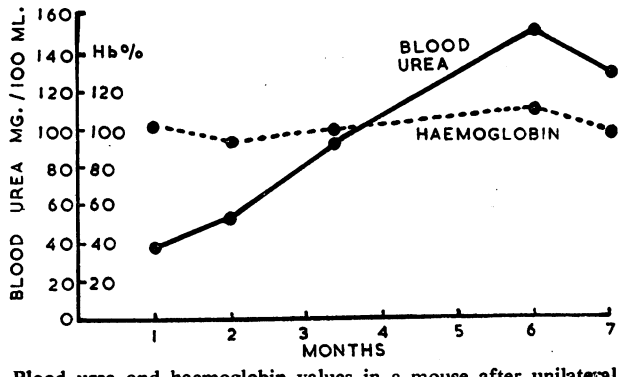
The anaemia caused by *x*-ray irradiation of the kidneys in mice was hypochromic to normochromic. The bone marrow showed a hypoplastic erythropoiesis.

In experiments with irradiation of the total amount of kidney tissue, the first changes observed were an increase of the blood urea level and a decrease in the haemoglobin values. Even at a time when the rise in blood urea was only from 20 to 23–24 mg. per 100 ml., a decrease in the haemoglobin value could be traced. It is therefore unlikely that the former caused the latter.

Through variation of the experimental procedure it has been possible to demonstrate the following.

1. In mice having a very small amount of kidney tissue shielded during the irradiation, the haemoglobin is maintained at a higher level than that usually found in connexion with the increased blood urea figures observed in these animals, and higher than in the animals with all the kidney tissue irradiated.

2. If one-quarter to one-third of one kidney is shielded during the irradiation the haemoglobin values may be maintained at the normal level, in spite of the development of



Blood urea and haemoglobin values in a mouse after unilateral nephrectomy and irradiation of approximately three-quarters of the remaining kidney with 8,000 r.

a considerable uraemia. The Chart shows the blood urea and the haemoglobin values in an animal which had been subjected to unilateral nephrectomy and irradiation of approximately three-quarters of the remaining kidney with 8,000 r. After six months the blood urea had reached 153 mg. per 100 ml., whereas the haemoglobin value was in the normal range, actually 111%.

3. Irradiation of one kidney and formation of an intraperitoneal outlet of the ureter from the other non-irradiated kidney is associated with normal haemoglobin values.

These experiments indicate that the failure of the kidney as an excretory organ and the development of the anaemia are parallel phenomena and independent of each other. These experiments also indicate that the kidney produces a principle of importance in erythropoiesis.

Table I gives the reticulocyte counts in (*a*) mice with both ureters ligated, (*b*) mice with total nephrectomy, (*c*) mice with partial nephrectomy, and (*d*) normal mice with intact kidneys. In all the groups acute anaemia was produced through bleeding. No reticulocyte reaction was found in the nephrectomized animals, whereas a reticulocytosis developed in the animals with ligated ureters. These observations correspond well with the findings of Jacobson *et al.*

TABLE I.—*Reticulocyte Count in Mice Bled ("Stimulus") in Connexion with Different Operations*

Operation	Stimulus	Reticulocytes %					Hb % 6 Days after Operation
		Before Operation	After Operation				
			12 Hours	24 Hours	2 Days	6 Days	
Ligation of ureters ..	Bleeding	2·7		4·7	Dead		
Total nephrectomy ..	,,	2·1	2·3	2·2	,,		
Partial nephrectomy (half a kidney left intact) .	,,	2·0	4·2	5·9	7·0	21·3	48
Controls. No operation	,,	2·9	6·5	13·0	13·2	32·1	50

Each group comprises three mice.

TABLE II.—*Reticulocyte Count in Serum-injected Mice*

Condition of Experimental Animals	Stimulus	Reticulocytes %					
		Before Serum Inj.	After Serum Injection				
			1 Day	4 Days	6 Days	8 Days	10 Days
(A) Uraemic mice with anaemia (irradiated kidneys)	"Activated" serum	2·7	6·3	7·8	8·4	6·2	
(B) Normal mice	,,	2·4		4·0	4·7	3·4	1·6
(C) Nephrectomized mice	Bleeding "activated" serum	2·6	4·3	Dead			
(D) Uraemic mice with anaemia (irradiated kidneys)	Ultra filtrate of "activated" serum	2·4		7·5	9·3	12·7	9·7

Each group includes three to five mice.

(1957), who studied the erythropoietic titre in rats and rabbits, nephrectomized or with ligated ureters. The reticulocyte reaction seemed to be stronger in the animals with intact kidneys than in those with reduced kidney substance.

Serum from bled normal mice ("activated" serum) injected into mice with anaemia after irradiation of their total kidney mass produces reticulocytosis. As shown in Table II A, the reticulocyte response is considerable, in spite of a severe uraemia and acidosis, even after a single injection of "activated" serum (0.3 ml.). These experiments show that the bone marrow of uraemic mice responds to an erythropoietic principle present in the blood of bled animals. This erythropoietic principle is able to counteract the anaemia caused by irradiation damage in kidneys.

"Activated" serum will also produce a reticulocyte response in normal mice with normal haemoglobin values (Table II B). This observation may explain the polycythaemia sometimes seen in connexion with renal tumours, and it may indicate that the principle observed may be a factor of importance also for the normal erythropoiesis.

As mentioned above, after an acute haemorrhage no reticulocyte response is found in nephrectomized mice. If the nephrectomized animals are injected with "activated" serum a reticulocyte response develops (Table II C).

Table II D summarizes the results of experiments with injection of protein-free ultrafiltrate from "activated" serum into mice with anaemia after irradiation of the kidneys. Also this protein-free filtrate contains an active principle.

Conclusion

An attempt has been made to demonstrate morphological structures, which may be related to the functional findings recorded above. In normal mouse kidneys stained with crystal violet and light green (Wilson, 1952) the juxtaglomerular cells show definite granules. In mice with anaemia produced through daily bleeding there is in some instances a distinct reduction of the number of granules in the juxtaglomerular cells and diminution of the individual granules.

Some months after unilateral nephrectomy and *x*-ray irradiation of the greater part of the other kidney no granules are found in the juxtaglomerular cells in the non-irradiated part of the kidney, and none or very few and small granules in the irradiated part. In bilaterally irradiated kidneys the granules in the juxtaglomerular cells are well preserved and the cells may even appear to be increased in size, with enlargement of the individual granules.

Further studies of the possible relationship between the alteration of the granules in the juxtaglomerular cells and the erythropoiesis are in progress.

ADDENDUM.—Since erythropoietin is regarded as a protein or a protein-bound non-filterable principle, and since the ultrafiltrate of "activated" serum is effective in anaemic mice with irradiation-induced nephritis but gives no reticulocytosis in normal mice, the indication is that the substance active in nephritic mice is different from erythropoietin. It can also be demonstrated that the serum from nephritic mice with anaemia can induce reticulocytosis in normal mice (erythropoietin effect). Further investigations indicate that the erythropoietic principle which is active in nephritic mice is connected to the granules of the juxtaglomerular cells. Such a substance may be referred to by the name of "juxtaglomerulin." A detailed account will be published later.

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A proposal that W.H.O. should be asked to consider organizing an International Public Health and Medical Research Year was unanimously endorsed by the U.N. General Assembly's social, humanitarian, and cultural committee in New York on November 12. The committee adopted a resolution under which the Assembly would invite W.H.O., in accordance with its agreement with the United Nations, to consider a recommendation to organize the Year and to adopt ways of intensifying international co-operation in health matters. Under the finally adopted resolution, the Assembly would state its desire to combat widely prevalent diseases such as malaria, tuberculosis, smallpox, cholera, cancer, cardiovascular ailments, leprosy, and poliomyelitis, and to solve other serious health problems. The resolution, after noting other fields of effort such as the use of atomic energy in medicine and popular health education where international co-operation might be intensified, invites W.H.O. to inform the next General Assembly session (in 1959) of its reaction to these proposals.